Original Article

Plasma Adiponectin Is Associated with Plasma Brain Natriuretic Peptide and Cardiac Function in Healthy Subjects

Takahiro OHARA¹⁾, Jiyoong KIM¹⁾, Masanori ASAKURA¹⁾, Hiroshi ASANUMA¹⁾,
Satoshi NAKATANI¹⁾, Kazuhiko HASHIMURA¹⁾, Hideaki KANZAKI¹⁾,
Tohru FUNAHASHI²⁾, Hitonobu TOMOIKE¹⁾, and Masafumi KITAKAZE¹⁾

The aim of this study was to evaluate the relationship between the plasma adiponectin level, plasma brain natriuretic peptide (BNP) level, and cardiac function in healthy subjects. We obtained clinical data and performed blood tests, including measurement of the plasma adiponectin and BNP levels, in 1,538 healthy persons from Arita-cho, a rural area of Japan. Six hundred and eight subjects also underwent echocardiography. There was a significant positive correlation between their plasma BNP and adiponectin levels in simple regression analysis (standardized regression coefficient [β]=0.34). Multivariate regression analysis revealed that the plasma adiponectin level was independently associated with the plasma BNP level (β =0.12), as well as with the age (β =0.22), male gender (β =−0.26), waist circumference (β =−0.16), and the plasma levels of high-density lipoprotein cholesterol (β =0.13), triglycerides (β =−0.16), aspartate aminotransferase (β =0.08), γ -glutamyl transpeptidase (β =−0.10), uric acid (β =−0.07), and creatinine (β =0.08). We also found a link between plasma adiponectin and the left atrial diameter index (β =0.08) or left ventricular diameter index (β =0.11), even after adjustment for age, sex, and body mass index. The plasma adiponectin level increased along with an increase of plasma BNP in healthy subjects independently of other confounding factors, demonstrating that adiponectin reflects cardiac function. (*Hypertens Res* 2008; 31: 825–831)

Key Words: adiponectin, brain natriuretic peptide, population based study, echocardiography

Introduction

Adiponectin is one of the circulating adipocytokines, and it plays a role in regulating insulin sensitivity, lipid metabolism, and systemic inflammation (1). The plasma adiponectin level is decreased in persons with obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome and ischemic heart disease (1–5). We and others have previously

reported that the severity of cardiac hypertrophy and subsequent heart failure is worsened in adiponectin knock-out mice subjected to pressure overload, suggesting that adiponectin may have a cardiovascular protective effect in patients with congestive heart failure (CHF) (6–8). Recent studies have indicated that the plasma adiponectin level is increased in patients with CHF, but the mechanism through which adiponectin production from adipose tissue is stimulated by CHF has not been elucidated (9, 10). The plasma brain natriuretic

From the ¹⁾Cardiovascular Division of Medicine, National Cardiovascular Center, Suita, Japan; and ²⁾Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Suita, Japan.

This study was supported by Grants-in-Aid for Research on the Human Genome, Tissue Engineering and Food Biotechnology (H13-Genome-011), Japanese Health and Labour Sciences Research Grants, and a Grant from the Japan Cardiovascular Research Foundation.

Address for Reprints: Masafumi Kitakaze, M.D., Ph.D., Cardiovascular Division of Medicine, National Cardiovascular Center, 5–7–1 Fujishirodai, Suita 565–8565, Japan. E-mail: kitakaze@zf6.so-net.ne.jp

Received July 27, 2007; Accepted in revised form November 27, 2007.

peptide (BNP) level has been reported to show a positive correlation with the plasma adiponectin level in patients with CHF or coronary heart disease (9–12). BNP secretion by the ventricular myocardium reflects the elevation of intracardiac pressure, and the circulating BNP level is related to the prognosis of CHF (13, 14). Even among apparently healthy subjects, relatively lower BNP levels predict a lower incidence of cardiovascular events, so BNP may reflect subtle hemodynamic changes in “healthy” persons (15). However, the relationship between plasma levels of BNP and adiponectin in healthy subjects has not yet been examined, and there has been no investigation of the relationship between the plasma adiponectin level and cardiac function.

To elucidate the factors predicting the plasma adiponectin level and to investigate the relationship between adiponectin and cardiac function, we performed a cross-sectional study of 1,538 healthy subjects without CHF from Arita-cho, a rural area in Japan. We investigated the predictors of adiponectin, including BNP, and also assessed the relationship between the plasma adiponectin level and echocardiographic parameters of cardiac function.

Methods

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the National Cardiovascular Center and that of Arita-cho. Written informed consent was obtained from each subject before participation in this study in accordance with approved institutional protocols.

Study Population

We studied 1,538 persons from Arita-cho who had no clinical evidence of overt CHF. Laboratory tests, including plasma adiponectin and BNP levels, were performed in all subjects and 608 of them also underwent echocardiography.

Assays

The plasma concentration of adiponectin was measured using a specific immunoradiometric assay (2). The plasma concentration of BNP was measured with a specific immunoradiometric assay for human BNP using a commercial kit (Shionoria; Shionogi Co., Ltd., Osaka, Japan) (14). The insulin resistance index was determined by the homeostasis model assessment of insulin resistance (HOMA-R) method (16).

Echocardiography

The left atrial diameter, the left ventricular end-diastolic and end-systolic dimensions, the left ventricular fractional shortening, and the left ventricular septal and posterior wall thickness were obtained by M-mode echocardiography. The left ventricular mean wall thickness was calculated by averaging

Table 1. Baseline Characteristics of 1,538 Subjects

Demographic data	
Age* (years)	62±15
Female/male (%)	63/37
Body mass index* (kg/m ²)	22±3
Waist circumference* (cm)	83±9
Concomitant diseases, % (n)	
Ischemic heart disease	3.4 (53)
Chronic atrial fibrillation	0.2 (3)
Hypertension	27 (408)
Diabetes mellitus	5.7 (88)
Hyperlipidemia	10 (160)
Hormonal status	
Adiponectin† (μg/mL)	10.6 (7.6–15.2)
BNP† (pg/mL)	18.0 (9.4–34.0)
Glucose metabolism	
Fasting blood glucose† (mg/dL)	83 (78–90)
Fasting insulin† (μU/mL)	4 (3–6)‡
HOMA-R†	0.9 (0.6–1.3)‡
Hemoglobin A1c* (%)	5.3±0.8
Lipids	
Total cholesterol* (mg/dL)	194±31
HDL cholesterol* (mg/dL)	55±12
Triglycerides† (mg/dL)	88 (63–122)
LDL cholesterol* (mg/dL)	119±29
Other parameters	
Hemoglobin* (g/dL)	13.4±1.5
AST† (IU/L)	22 (19–26)
ALT† (IU/L)	18 (14–23)
γ-GTP† (IU/L)	22 (16–37)
Uric acid* (mg/dL)	4.9±1.4
Creatinine* (mg/dL)	0.9±0.2
Blood pressure	
SBP* (mmHg)	128±20
DBP* (mmHg)	77±11
MBP* (mmHg)	94±13

BNP, brain natriuretic peptide; HOMA-R, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. *Values are shown as the mean±SD. †Values are shown as the median (interquartile range). ‡n=800.

the left ventricular septal and posterior wall thickness. All echocardiograms were read by physicians from the National Cardiovascular Center who were blinded to any clinical information about the subjects. Indexed values were calculated by dividing the results by the body surface area, which was calculated according to Mosteller (17). The left ventricular mass was calculated using parameters measured by M-mode echocardiography (18). Mitral inflow was assessed in the api-

Fig. 1. Scatter plot of the association between log-transformed plasma adiponectin and plasma BNP levels in apparently healthy subjects from Arita-cho. Lines indicate the regression line (thick line) and 95% confidence interval (thin lines). BNP, brain natriuretic peptide; β , standardized regression coefficient.

cal four-chamber view using pulsed-wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of the flow and the sample volume set at the leaflet tips. From the mitral inflow profile, the peak velocity of early diastolic transmitral flow, the peak velocity of late diastolic transmitral flow, and the early diastolic transmitral flow deceleration time were measured (19).

Statistical Analysis

Numerical data are reported as the mean $\pm$ SD or the median and interquartile range, as appropriate. Data on the levels of adiponectin, BNP, fasting insulin, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ -glutamyl transpeptidase (γ -GTP) were logarithmically transformed for linear regression analysis. Multivariate analysis was done to examine the correlations of log-transformed adiponectin levels with the variables that were associated with adiponectin ($p < 0.10$) according to simple regression analysis. The final model always included the following potentially confounding variables irrespective of the results of univariate analysis; age, sex, body mass index (BMI), ischemic heart disease, and atrial fibrillation. Fasting insulin levels and HOMA-R were not included in the final model because of missing data for a significant number of subjects.

Echocardiographic parameters were assessed for their relationship with adiponectin (log-transformed) by univariate analysis or analysis adjusted for age, gender, and BMI. Interaction effects of gender, age (65 years or older), ischemic heart disease, hypertension, diabetes mellitus, and hyperlipidemia on the relation between plasma adiponectin and BNP levels were examined with analysis of covariance. A probability (p) value < 0.05 was accepted as indicating statistical significance unless otherwise mentioned. A software package (SPSS 10.0.5J; SPSS, Chicago, USA) was used for statistical analysis.

Results

The profile of the subjects is shown in Table 1. There was a significant positive correlation between their plasma BNP and adiponectin levels (Fig. 1). This relationship was not influenced by covariates such as gender, age (65 years or older), ischemic heart disease, hypertension, diabetes mellitus, or hyperlipidemia.

Predictors of the Adiponectin Level

Table 2 shows the factors from among clinical, laboratory, and hemodynamic parameters that showed correlations with the plasma adiponectin levels. Univariate analysis revealed that male sex and diabetes mellitus were associated with lower adiponectin levels. The BMI, waist circumference, fasting blood glucose, fasting insulin, HOMA-R, triglycerides, hemoglobin, ALT, γ -GTP, uric acid, creatinine, and blood pressure were all negatively correlated with the plasma adiponectin level, whereas age, plasma BNP, and plasma high-density lipoprotein (HDL)-cholesterol were positively correlated with adiponectin. Among these factors, it was found that male sex, waist circumference (but not BMI), and the plasma levels of triglycerides, AST, γ -GTP, and uric acid were negatively correlated with adiponectin by multivariate analysis, while there were positive correlations for age and the plasma levels of BNP, HDL-cholesterol, and creatinine. In the present cross-sectional study, sex was most strongly associated with the plasma adiponectin level, followed by age, according to the standardized regression coefficients (β). The plasma BNP level showed as strong an association with the plasma adiponectin level as did waist circumference, HDL-cholesterol, and triglycerides.

Echocardiographic Parameters

Since the plasma adiponectin level is elevated in patients with heart failure, we examined whether adiponectin was related to cardiac function. The baseline echocardiographic parameters are displayed in Table 3.

According to univariate analysis (Table 4), several echocardiographic parameters were related to the plasma adiponectin level, including the left atrial diameter index, left ventricular

Table 2. Factors Correlated with Plasma Adiponectin by Regression Analysis

	Univariate		Multivariate	
	Standardized coefficient	<i>p</i> value	Standardized coefficient	<i>p</i> value
<i>r</i> ² of the test			0.40	<0.0001
Age	0.26	<0.0001	0.22	<0.0001
Male sex	−0.38	<0.0001	−0.26	<0.0001
Body mass index	−0.27	<0.0001	−0.05	0.2247
Waist circumference	−0.29	<0.0001	−0.16	0.0001
Ischemic heart disease	0.01	0.6838		
Hypertension	<0.01	0.9972		
Diabetes	−0.06	0.0230	<0.01	0.9911
Hyperlipidemia	<0.01	0.8449		
Log BNP	0.34	<0.0001	0.12	<0.0001
Fasting blood glucose	−0.08	0.0440	−0.04	0.0716
Log fasting insulin*	−0.22	<0.0001		
HOMA-R*	−0.15	<0.0001		
Hemoglobin A1c	−0.04	0.3020		
Total cholesterol	0.02	0.5580		
HDL-cholesterol	0.26	<0.0001	0.13	<0.0001
Log triglycerides	−0.29	<0.0001	−0.16	<0.0001
LDL-cholesterol	0.05	0.2140		
Hemoglobin	−0.42	<0.0001	−0.05	0.0811
Log AST	−0.07	0.0810	0.08	0.0206
Log ALT	−0.29	<0.0001	−0.03	0.3611
Log γ -GTP	−0.25	<0.0001	−0.10	0.0004
Uric acid	−0.29	<0.0001	−0.07	0.0114
Creatinine	−0.16	<0.0001	0.08	0.0050
SBP	−0.01	0.7480		
DBP	−0.08	0.0470		
MBP	−0.08	0.0029	0.04	0.1077

BNP, brain natriuretic peptide; HOMA-R, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GTP, γ -glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. *Log fasting insulin and HOMA-R were not included in the multivariate model, because insulin was not measured in a considerable number of subjects.

Table 3. Echocardiographic Data Obtained in 608 Subjects

Left atrial diameter (mm)	37 (33–41)
Left atrial diameter index (mm/m ²)	24 (22–27)
Left ventricular end-diastolic diameter (mm)	46 (43–50)
Left ventricular end-diastolic diameter index (mm/m ²)	30 (28–33)
Fractional shortening (%)	40 (35–45)
Mean wall thickness (mm)	9 (8–10)
Left ventricular mass (g)	140 (114–166)
Left ventricular mass index (g/m ²)	90 (76–106)
E wave velocity (cm/s)	63 (53–74)
A wave velocity (cm/s)	77 (64–89)
E/A ratio	0.82 (0.69–0.99)
Deceleration time (ms)	217 (192–258)

Values are shown as the median (interquartile range). E, early diastolic transmitral flow; A, late diastolic transmitral flow.

end-diastolic diameter index, the fractional shortening, the mean wall thickness, the left ventricular mass index, the late diastolic transmitral flow velocity, and the early/late diastolic transmitral flow velocity ratio. After adjustment for age, sex and BMI, however, only the left atrial diameter index and the left ventricular end-diastolic diameter index were positively correlated with the circulating adiponectin level.

Discussion

The present study demonstrated that the plasma adiponectin level was positively correlated with the plasma BNP level in healthy subjects along with known predictors such as the age, BMI, waist circumference, HDL-cholesterol, triglycerides, liver function parameters, uric acid, and renal function parameters. The plasma BNP level had the same influence on adiponectin as that of the waist circumference, HDL-cholesterol, and triglycerides. We also demonstrated that the plasma adi-

Table 4. Factors Correlated with the Plasma Level of Adiponectin in Regression Analysis

	Univariate		Adjusted for age, sex, and BMI	
	Standardized coefficient	<i>p</i> value	Standardized coefficient	<i>p</i> value
Left atrial diameter	−0.09	0.0326	0.05	0.2528
Left atrial diameter index	0.24	<0.0001	0.08	0.0312
Left ventricular end-diastolic diameter	−0.16	0.0001	0.06	0.1035
Left ventricular end-diastolic diameter index	0.30	<0.0001	0.11	0.0045
Fractional shortening	0.09	0.0354	−0.03	0.4557
Mean wall thickness	−0.09	0.0266	−0.02	0.6545
Left ventricular mass	−0.17	<0.0001	0.03	0.4725
Left ventricular mass index	0.02	0.6362	0.05	0.2028
E wave velocity	−0.01	0.8528	<0.01	0.9886
A wave velocity	0.15	0.0003	−0.01	0.8500
E/A ratio	−0.13	0.0013	0.02	0.6726
Deceleration time	0.06	0.1439	0.01	0.7182

BMI, body mass index; E, early diastolic transmitral flow; A, late diastolic transmitral flow.

ponectin level reflects cardiac function to some extent, even in apparently healthy subjects.

Link between Plasma Adiponectin and BNP

The plasma adiponectin level is reported to be increased and to show a positive correlation with plasma BNP in CHF patients (9, 10). It has been suggested that cardiac cachexia due to the progression of heart failure leads to an increase of plasma adiponectin levels (7). However, this study revealed that “healthy” subjects without cardiac cachexia also demonstrated a positive correlation between plasma adiponectin and BNP levels, suggesting that cardiac cachexia itself is unlikely to be the reason for the positive relationship between plasma adiponectin and BNP levels.

In obese patients, BNP levels are lower, due to increased expression of the natriuretic clearance receptor in adipose tissue or some other unknown factor (20). Because adiponectin levels are also lower in obese patients, one may argue that the relationship between the plasma adiponectin and BNP is confounded by obesity (2). Renal dysfunction is known to increase the levels of both adiponectin and BNP (21, 22). However, the influence of obesity and renal dysfunction cannot explain the adiponectin-BNP relationship that was revealed by the present observational study, which found a tight relationship between plasma adiponectin and BNP independently of these potentially confounding factors.

The final possibility is that BNP directly increases adiponectin production. Indeed, we have preliminary data showing that BNP directly increases adiponectin mRNA expression in cultured 3T3-L1 adipocytes (data not shown). Wang *et al.* reported that low BNP was associated with metabolic risk factors in ambulatory individuals (23), and that these risk factors could be mediated by adiponectin, which was consistent with a tight linkage between adiponectin and BNP levels. Higher levels of adiponectin could constitute a

risk for CHF, and at the same time could be a negative risk for metabolic syndrome through their interaction with BNP; lower levels of BNP could constitute a negative risk for CHF and at the same a risk for metabolic syndrome through their interaction with adiponectin.

Adiponectin and Cardiac Function

Wang *et al.* reported that the extent of the increase in plasma BNP levels could predict cardiovascular mortality in subjects without CHF, indicating that subtle stress on the heart can be detected by monitoring BNP and this stress leads to cardiovascular events (15).

We demonstrated that some conventional echocardiographic parameters (left atrial and left ventricular diameter indexes) showed a relationship with adiponectin similar to the relation of BNP to adiponectin. Previous studies of the relationship between adiponectin and BNP have also found no obvious cardiac dysfunction in their subjects, but they did not examine echocardiographic parameters (11, 12).

Cardiac dimensions are not direct indexes of cardiac function. However, it is also the case that left ventricular dimensions are tightly related to cardiac function. As cardiac function is depressed, end-diastolic or systolic ventricular dimension increases, and vice versa. Even subjects with high-normal blood pressure suffer from some degree of left ventricular remodeling (24). The left atrial dimension, a predictor of atrial fibrillation, reflects blood pressure levels and metabolic abnormalities in ambulatory settings (25). Plasma adiponectin may increase to counteract these latent cardiac remodeling effects.

How does hemodynamics or structural change regulate adiponectin production? One possibility is that BNP directly causes an increase of adiponectin production, as mentioned above. Alternatively, there is a possibility that adiponectin is produced in the heart when it is placed under stress. It has

been reported that adiponectin is synthesized and secreted by isolated murine and human cardiomyocytes (26). However, the production of adiponectin by adipose tissue is greater than that by cardiac tissue (in part because the amount of adipose tissue is greater), suggesting that most of the circulating adiponectin is derived from adipose tissue.

Cardioprotective Role of BNP and Adiponectin

BNP is known to have a protective effect against cardiovascular injury *via* the cyclic GMP-G kinase pathway, and an increase of BNP is believed to improve the severity of heart failure (14, 27, 28). BNP may exert a cardioprotective effect on subclinical heart disease (15).

We and another group have recently reported that cardiac hypertrophy and subsequent heart failure are accelerated by aortic banding in adiponectin knock-out mice (6, 8). Cardiac hypertrophy is believed to be a major risk factor for cardiovascular death, suggesting that adiponectin release is increased by stresses acting on the heart even in healthy subjects for prevention of cardiac injury like BNP (29). Adiponectin may decrease the onset or the progression of CHF. Pioglitazone has been reported to increase adiponectin production *via* stimulation of peroxisome proliferator-activated receptor γ and it also reduces cardiac hypertrophy in mice with aortic banding (30). Thus, adiponectin may be a target for prevention of overt CHF.

Clinical Implications

The positive correlation between plasma adiponectin and BNP levels in apparently healthy individuals in our study suggests that adiponectin can predict a worsening of prognosis or morbidity of heart failure even in healthy subjects. In addition, we need to consider whether latent heart failure and BNP levels should be taken into account when we examine subjects with higher adiponectin levels in clinical settings. Further prospective investigations are therefore warranted to determine whether high adiponectin levels are related to worse prognosis or future morbidity of heart failure even in healthy subjects.

Limitations

The present large-scale cross-sectional study showed a close relationship between adiponectin and BNP. However, the nature of a cross-sectional study means that we could not assess the prognostic impact of adiponectin in our healthy subjects. In CHF patients, high adiponectin levels are related to a worse prognosis, so longitudinal studies are needed to elucidate the impact of adiponectin on the prognosis in apparently healthy persons (9, 10).

We used self-administered questionnaires to investigate the rates of risk factors and the current state of treatment. The percentages of subjects taking medication were 81%, 61%,

and 68% for the patients with hypertension, diabetes mellitus, and hyperlipidemia, respectively. There were no significant differences in adiponectin and BNP values between those taking and those not taking medications. Thus medications do not seem to have influenced the results significantly.

Conclusions

The plasma adiponectin level increased along with an increase of the plasma BNP level in apparently healthy subjects, suggesting that plasma adiponectin reflects some aspects of cardiac function.

Acknowledgements

We would like to thank the following groups and individuals, whose cooperation was essential in the design and implementation of this project: the staff of the Department of Healthcare, Arita Town, Saga, Japan; and Go Ichien, Yumi Itoh and the staff of HuBit Genomix, Inc. We would also like to acknowledge the statistical advice of Akiko Kada, MPH (National Cardiovascular Center, Suita, Japan).

References

1. Santaniemi M, Kesaniemi YA, Ukkola O: Low plasma adiponectin concentration is an indicator of the metabolic syndrome. *Eur J Endocrinol* 2006; **155**: 745–750.
2. Arita Y, Kihara S, Ouchi N, *et al*: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257**: 79–83.
3. Hotta K, Funahashi T, Arita Y, *et al*: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1595–1599.
4. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P: Adiponectin: a key adipocytokine in metabolic syndrome. *Clin Sci (Lond)* 2006; **110**: 267–278.
5. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; **291**: 1730–1737.
6. 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.
7. Ouchi N, Shibata R, Walsh K: Cardioprotection by adiponectin. *Trends Cardiovasc Med* 2006; **16**: 141–146.
8. Shibata R, Ouchi N, Ito M, *et al*: Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat Med* 2004; **10**: 1384–1389.
9. George J, Patal S, Wexler D, *et al*: Circulating adiponectin concentrations in patients with congestive heart failure. *Heart* 2006; **92**: 1420–1424.
10. Kistorp C, Faber J, Galatius S, *et al*: Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005; **112**: 1756–1762.
11. Pilz S, Mangge H, Wellnitz B, *et al*: Adiponectin and mortality in patients undergoing coronary angiography. *J Clin*

- Endocrinol Metab* 2006; **91**: 4277–4286.
12. von Eynatten M, Hamann A, Twardella D, Nawroth PP, Brenner H, Rothenbacher D: Relationship of adiponectin with markers of systemic inflammation, atherogenic dyslipidemia, and heart failure in patients with coronary heart disease. *Clin Chem* 2006; **52**: 853–859.
 13. 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.
 14. Tsutamoto T, Wada A, Maeda K, et al: Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; **96**: 509–516.
 15. Wang TJ, Larson MG, Levy D, et al: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350**: 655–663.
 16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
 17. Mosteller RD: Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**: 1098.
 18. Devereux RB, Alonso DR, Lutas EM, et al: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.
 19. Kitabatake A, Inoue M, Asao M, et al: Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease—a study by pulsed Doppler technique. *Jpn Circ J* 1982; **46**: 92–102.
 20. Wang TJ, Larson MG, Levy D, et al: Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004; **109**: 594–600.
 21. Tsutamoto T, Wada A, Sakai H, et al: Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2006; **47**: 582–586.
 22. Zoccali C, Mallamaci F, Tripepi G, et al: Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002; **13**: 134–141.
 23. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS: Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. *Circulation* 2007; **115**: 1345–1353.
 24. Kimura Y, Tomiyama H, Nishikawa E, et al: Characteristics of cardiovascular morphology and function in the high-normal subset of hypertension defined by JNC-VI recommendations. *Hypertens Res* 1999; **22**: 291–295.
 25. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D: Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension* 1995; **25**: 1155–1160.
 26. Pineiro R, Iglesias MJ, Gallego R, et al: Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett* 2005; **579**: 5163–5169.
 27. D'Souza SP, Yellon DM, Martin C, et al: B-type natriuretic peptide limits infarct size in rat isolated hearts via KATP channel opening. *Am J Physiol Heart Circ Physiol* 2003; **284**: H1592–H1600.
 28. Nishikimi T, Maeda N, Matsuoka H: The role of natriuretic peptides in cardioprotection. *Cardiovasc Res* 2006; **69**: 318–328.
 29. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561–1566.
 30. Asakawa M, Takano H, Nagai T, et al: Peroxisome proliferator-activated receptor gamma plays a critical role in inhibition of cardiac hypertrophy *in vitro* and *in vivo*. *Circulation* 2002; **105**: 1240–1246.