Differential Association of Adiposity Measures with Heart Rate Variability Measures in Koreans

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Received: February 14, 2012
Revised: March 23, 2012
Accepted: March 24, 2012
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- The authors have no financial conflicts of interest.

Purpose: Although obesity has been associated with imbalances in cardiac autonomic nervous system, it is unclear whether there are differential relationships between adiposity measures and heart rate variability (HRV) measures. We aimed to examine differences in the relationship between adiposity measures and HRV indices in a healthy Korean population. Materials and Methods: In all, 1409 non-smokers (811 males, 598 females) without known histories of cardiovascular (CV), endocrine, or neurological diseases underwent adiposity measurements [(body mass index (BMI), percentage of body fat mass (PBF), and waist-to-hip ratio (WHR)], the HRV assessment (SDNN, RMSSD, LF, HF, LF/HF, and pNN50), and examination for CV risk factors (fasting glucose, LDL-cholesterol, HDL-cholesterol, triglycerides, hs-CRP, and blood pressure). Results: Compared with BMI and PBF, WHR was more strongly correlated with each HRV index and more likely to predict decreased HRV (<15 percentile vs. ≥15 percentile of each HRV index) in ROC curves analysis. In linear regression analysis, all adiposity measures were inversely associated with each HRV measure before adjusting for age, gender, and CV risk factors ($p<0.05$). After adjusting for the covariates, WHR was inversely related to RMSSD, LF, and pNN50; PBF with RMSSD, HF, and pNN50; BMI with RMSSD ($p<0.05$). The inverse association between HRV indices and the gender-specific WHR tertile was significant for subjects with BMI ≥25 kg/m$^2$, but not for those with BMI <25 kg/m$^2$. Conclusion: WHR and PBF appear to be better indicators for low HRV than BMI, and the association between abdominal adiposity and HRV may be stronger in overweight subjects.

Key Words: Heart rate variability, adiposity, abdominal fat, cardiac autonomic function, obesity

INTRODUCTION

The autonomic nervous system (ANS) is an important regulator of both energy balance and the cardiovascular system, and it is thought to contribute to the pathophysiology of obesity. Increased adiposity has been linked to decreased sympathetic responsiveness, the alteration of both sympathetic and parasympathetic activi-
ties,1,4,5 and decreased isolated parasympathetic activity.6
Decreased adiposity after weight reduction has also been
associated with improved ANS function.5,12 However, dif-
erential relationships between adiposity measures reflect-
ing overall adiposity or abdominal fat with ANS activity re-
main inconclusive. Considerably varied results have been
reported in the studies which compared overall adiposity
and abdominal adiposity with a risk of cardiovascular dis-
ease and mortality.13,14 Although the mechanisms underlying
these associations are still unclear, it is thought that dif-
fferences in metabolic activity between adipose tissues in
visceral fat and subcutaneous fat play an important role.15 It
would follow, therefore, that the relationship between adi-
posity and ANS activity would not be consistent for differ-
ent measures of adiposity that consider abdominal versus
overall adiposity.

In addition, as these relationships have been examined in
a small number of case-control or cross-sectional studies,3-12
knowledge about these relationships in a large number of
samples across wide range of weights and conventional
cardiovascular (CV) risk factors is limited.16

The heart rate variability (HRV) has been applied to eval-
uate ANS function using time-domain and frequency-do-
main measures, and decreased HRV has been considered a
risk factor of CV mortality and morbidity.5,17 As the HRV is
a non-invasive and reliable method, it has been used in a
variety of clinical situations including obesity. In the pres-
et study, our goal was to compare the relationships be-
tween cardiac ANS function, measured by the HRV, and
three adiposity measures that reflect overall or abdominal
adiposity in apparently healthy Korean adults, and to evalu-
ate these relationships according to weight subgroup.

MATERIALS AND METHODS

Study population
A total of 1409 Korean adults (811 males, 598 females) were
recruited from the Center of Health Promotion at a university
hospital from January 2004 to March 2005. None of the
subjects were current smokers or had a self-reported med-
cal history of any diseases that have potential of disturb-
ging autonomic cardiac function. Informed consent was
obtained from each participant. The study protocol was ap-
proved by the Institutional Review Board of the Yeungnam
University Hospital.

To regulate the physiologic and environmental variations,
raw ECG signals were recorded for 10 minutes in the
morning and in the overnight fasting state while each sub-
ject lays quietly. They were asked to breathe normally in a
quiet environment. Subjects took medical examination be-
fore the HRV assessment. ECG signals were digitized by
using an analog-to-digital converter with a sampling rate of
1 KHz and were stored on a hard disk for off-line analysis
(MP 150 and AcqKnowledge ver 3.5, Biopac Systems,
Santa Barbara, CA, USA).

Using the method of R-peak detection algorithm from
different ECG signals and preprocessing procedures, HRV
was extracted and the ECG recordings including noise and
non-sinus beats that were more than 1% of the total number
of beats were not used for HRV extraction. Premature beats
and artifacts were carefully eliminated manually by a visual
inspection of all RR intervals. Stationary HRV signals of 5
minutes duration were finally adopted from each subject for
a reliable analysis of HRV.18

The time domain analysis of HRV included the standard
deviations of all R-R intervals (SDNN), the square root of
the mean squared differences of successive normal sinus in-
tervals (RMSSD), and the percentage of successive RR in-
terval differences whose absolute value exceeds 50 ms
(pNN50).19,20 The frequency domain analysis included the
low frequency (LF) spectral power component and the high
frequency (HF) spectral component. The LF was defined as
the power between 0.04 and 0.15 Hz, and HF was defined as
the power between 0.15 and 0.4 Hz bands under the power
spectral density curve. LF to HF ratio (LF/HF) was comput-
ed.18,21,22 The SDNN presents parasympathetic activity as
well as the sympathetic activity of heart function, while
RMSSD reflects predominantly vagal function. The LF and
HF components are considered an index of sympathetic
and parasympathetic modulation, respectively and then, the
LF to HF ratio reflects the global sympatho-vagal balance.18,21

The body mass index (BMI) was calculated using mea-
sured body weight (kg) divided by measured height (m) in
squared. The percentage of body fat mass (PBF) and waist-
to-hip ratio (WHR) were measured by segmental bioelectri-
cal impedance using eight tactile electrodes, according to
the manufacturer’s instructions (In Body 2.0; Biospace,
Seoul, Korea).23 For metabolic CV risk factors, blood pres-
sure (BP) and biochemical factors were assessed. To mea-
sure biochemical factors, venous blood was drawn after an
overnight fast. Plasma glucose was assayed using a hexoki-
nase enzymatic method. Serum low-density lipoprotein
cholesterol, high-density lipoprotein cholesterol, and tri-
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glycerides were assayed using homogeneous and enzymatic methods. High sensitivity C-reactive protein (hs-CRP) was assayed using latex immune complex turbidimetry. BP measurements were obtained twice with a manual sphygmomanometer with the participants in the sitting position, and the average of two measurements was used for analysis.

Statistical analyses
A natural logarithmic transformation was applied to normalize the distribution of SDNN, RMSSD, LF, and HF values. We applied linear regression analyses to evaluate a linear trend in the relationships of gender-specific tertiles of SDNN with adiposity measures and metabolic CV risk factors. We computed Spearman correlations between the adiposity measures and HRV indices, and compared statistical significance of the difference between two correlation coefficients. We also compared three adiposity measures in predicting low HRV (<15 percentile vs. ≥15 percentile of each HRV measure) using receiver operating characteristics (ROC) curve analysis. We used multiple linear regression models to find associations between each HRV index and z-score of each adiposity measure after adjusting for age and gender or adjusting for age, gender, and CV risk factors. The multiple linear regression models were also used to find a linear trend of HRV index according to gender-specific WHR tertiles in weight subgroups (BMI <25 kg/m² vs. BMI ≥25 kg/m²) after adjusting for age, gender, and CV risk factors. These analyses were performed using PASW, Statistics18 [Release 18.0.0 (30 July. 2009); SPSS Inc., Chicago, IL, USA] and MedCalc Version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS
Of the 1409 subjects, 476 (33.4%) and 26 (1.8%) had BMI ≥25 kg/m² and BMI ≥30 kg/m², respectively. When the associations of SDNN tertile with adiposity measures and CV risk factors were evaluated, three adiposity measures and values of CV risk factors significantly decreased with increasing tertiles of SDNN (Table 1). As shown in Table 2, the inverse correlations between each adiposity measure and each HRV index were all significant. When the magnitudes of two correlation coefficients were compared, the

Table 1. Associations between Adiposity and Heart Rate Variability Measures and Cardiovascular Risk Factors with Sex-Specific ln SDNN Tertiles

|                          | Overall          | Lowest third M: 2.1-3.4 ms F: 1.7-3.3 ms | Middle third M: 3.4-3.9 ms F: 3.3-3.7 ms | Highest third M: 3.9-6.1 ms F: 3.7-5.0 ms | p for trend* |
|--------------------------|------------------|------------------------------------------|------------------------------------------|------------------------------------------|-------------|
| Age (yrs)                | 48.0 (12.3)      | 53.4 (11.3)                              | 47.8 (11.3)                              | 42.7 (12.0)                              | <0.001      |
| Body mass index (kg/m²)  | 23.7 (2.9)       | 24.1 (2.9)                               | 23.8 (2.9)                               | 23.3 (2.9)                               | <0.001      |
| % body fat mass (%)      | 24.3 (6.2)       | 25.3 (6.4)                               | 24.2 (6.1)                               | 23.7 (6.1)                               | <0.001      |
| Waist-to-hip ratio       | 0.89 (0.05)      | 0.91 (0.05)                              | 0.89 (0.05)                              | 0.88 (0.05)                              | <0.001      |
| ln RMSSD (ms)            | 3.2 (0.6)        | 2.6 (0.5)                                | 3.1 (0.4)                                | 3.7 (0.5)                                | <0.001      |
| ln LF (ms²)              | 5.9 (1.3)        | 4.7 (0.7)                                | 5.9 (0.7)                                | 7.2 (0.9)                                | <0.001      |
| ln HF (ms²)              | 5.2 (1.3)        | 4.2 (0.9)                                | 5.1 (0.8)                                | 6.2 (1.0)                                | <0.001      |
| pNN50 (%)                | 9.5 (14.0)       | 0.9 (2.6)                                | 5.5 (7.5)                                | 22.1 (16.7)                              | <0.001      |
| ln LF/HF                 | 0.7 (1.1)        | 0.5 (0.9)                                | 0.7 (1.1)                                | 0.9 (1.2)                                | <0.001      |
| Systolic BP (mm Hg)      | 121.7 (13.0)     | 125.5 (13.6)                             | 120.8 (12.4)                             | 118.9 (12.0)                             | <0.001      |
| Diastolic BP (mm Hg)     | 77.2 (9.1)       | 79.5 (9.5)                               | 76.8 (8.6)                               | 75.3 (8.7)                               | <0.001      |
| Fasting glucose (mg/dL)  | 92.8 (20.2)      | 97.8 (25.8)                              | 91.0 (14.7)                              | 89.5 (17.3)                              | <0.001      |
| LDL cholesterol (mg/dL)  | 115.3 (32.1)     | 119.3 (32.2)                             | 114.1 (31.7)                             | 112.5 (32.1)                             | 0.003       |
| HDL cholesterol (mg/dL)  | 56.6 (13.5)      | 55.5 (13.2)                              | 56.2 (13.6)                              | 57.9 (13.6)                              | 0.018       |
| Triglycerides (mg/dL)    | 130.6 (85.3)     | 141.7 (83.5)                             | 132.7 (92.0)                             | 117.4 (78.4)                             | <0.001      |
| hs-CRP (mg/dL)           | 0.17 (0.44)      | 0.23 (0.63)                              | 0.17 (0.38)                              | 0.12 (0.23)                              | <0.001      |

M, male; F, female; ln, natural logarithm; SDNN, standard deviation of all normal RR intervals; RMSSD, root mean square of successive differences; LF, low frequency power; HF, high frequency power; pNN50, percentage of differences between adjacent RR intervals that are greater than 50 ms; LF/HF, ratio of the low/high frequency power; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high sensitivity C-reactive protein.

Values are presented as mean (SD). To convert to SI units, multiply by 0.0259 for LDL and HDL cholesterol (mmol/L) and by 0.0113 for triglycerides (mmol/L).

*Analyzed using linear regression test.
correlations between WHR and HRV measures were generally stronger than the correlations for BMI or PBF \((p<0.05)\). The correlations between PBF and HRV measures (SDNN, LF, and LF/HF) were even stronger than the correlations for BMI \((p<0.05)\). The difference between adiposity measures in the relations with HRV indices was also found when ROC curves analysis was conducted to compare the three adiposity measures for predicting lower HRV \((i.e., <15\text{th} \text{ percentile vs. } \geq 15\text{th} \text{ percentile of each HRV index})\). WHR was more likely to predict lower SDNN, RMSSD, LF, HF, and pNN50 than BMI and PBF \((p<0.05)\) (Table 3).

In the multivariable adjusted models, the difference in the associations between the three adiposity measures and HRV measures remained. Table 4 summarizes the magnitude of change of these associations with adjustment for covariates among the three adiposity measures. After adjusting for age and gender, the magnitudes of associations between these variables were attenuated, but these associations were still significant. When the associations were further adjusted for CV risk factors, BMI was associated only with LF, but not with other HRV measures \((p<0.05)\). By comparison, WHR and PBF consistently had independent and inverse associations with HRV indices (RMSSD, LF, and pNN50 for WHR and RMSSD, HF, and pNN50 for PBF). When the linear trend of HRV index according to gender-specific WHR tertile was evaluated in weight subgroups, SDNN, RMSSD, LF, HF, and pNN50 decreased with increasing gender-specific WHR tertiles in the overweight subgroup, but not in the non-overweight subgroup (Fig. 1).

**DISCUSSION**

In this large cross-sectional samples of apparently healthy Korean adults, we found that three adiposity measures reflecting either general or abdominal adiposity were differentially associated with the HRV measures. WHR was more likely than BMI or PBF to be strongly associated with almost all of the HRV indices that are thought to be modulated by both the sympathetic and parasympathetic nervous systems. In addition, these associations were significant when age, gender, and CV risk factors were considered, and they were only significant in the overweight subgroup. Increased PBF, reflecting overall fat, also appeared to be a

| Correlation coefficient | Body mass index (kg/m\(^2\)) | % body fat mass (%) | Waist-to-hip ratio |
|-------------------------|-------------------------------|---------------------|--------------------|
| SDNN (ms)               | -0.09*                        | -0.18*†             | -0.24*‡            |
| RMSSD (ms)              | -0.11*                        | -0.16*              | -0.26*‡            |
| LF (ms\(^2\))           | -0.10*                        | -0.20*†             | -0.28*‡            |
| HF (ms\(^2\))           | -0.10*                        | -0.12*              | -0.25*‡            |
| pNN50 (%)               | -0.11*                        | -0.13*              | -0.22*‡            |
| LF/HF                   | -0.01                         | -0.10*†             | -0.05              |

In, natural logarithm; SDNN, standard deviation of all normal RR intervals; RMSSD, root mean square of successive differences; LF, low frequency power; HF, high frequency power; pNN50, percentage of differences between adjacent RR intervals that are greater than 50 ms; LF/HF, ratio of the low/high frequency power.

*\(p<0.01\), Spearman correlation between each adiposity measure and HRV index.

†\(p<0.05\), comparison of two correlation coefficients (% body fat mass vs. body mass index, or waist-to-hip ratio vs. body mass index).

‡\(p<0.05\), comparison of two correlation coefficients (% body fat mass vs. waist-to-hip ratio).

**Table 2. The Spearman Correlation between Adiposity Measure and Heart Rate Variability (HRV) Index**
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...activity and higher parasympathetic activity compared with non-obese controls.

2 Similarly, a decrease in HRV was found in morbidly obese group compared with controls in 80 women, and significant associations between metabolic and hormonal factors and HRV measures disappeared after adjusting for body fat mass.

5 It has also been suggested that HRV is reversible. In a handful of studies about change in ANS activity after weight loss in obese patients, an increase in HRV was noted after weight loss by gastroplasty,

7 increased physical activity and calorie restriction,

8-10 and anti-obesity medication.

11 An association between abdominal fat and ANS imbalance has also been reported. Lindmark, et al.24 reported that there was a positive association between visceral abdominal fat and sympathetic/parasympathetic ratio in HRV assessment, while subcutaneous abdominal fat was not associated with HRV measures in 18 subjects, including first-degree relatives of patients with type 2 diabetes and controls. A positive association between intra-abdominal adiposity and sympathetic activity was also found among

better predictor for decreased HRV indices than BMI, which does not discriminate fat from muscle. Therefore, increased abdominal fat appeared to be an independent indicator of decreased ANS balance regardless of age, gender, and CV risk factors, particularly in the overweight subgroup. Additionally, abdominal fat is a better predictor of low HRV than overall fat.

In previous studies, associations between obesity and low HRV were reported mainly in small case-control or cross-sectional studies. Our findings extend this knowledge to a population comprised of many people of normal weight and a small subgroup of obese participants (1.8% had a BMI of >30 kg/m²). Laederach-Hofmann, et al.1 showed that BMI and WHR were inversely correlated with sympathetic activity in 42 subjects with a BMI of 28-83 kg/m². Associations between body fat percentage and depression in sympathetic and parasympathetic activity were also found in 56 men with various percentages of body fat.4 In an another study with 44 obese patients and normal-weight controls, obese patients had HRV indices reflecting lower sympathetic activity and higher parasympathetic activity compared with non-obese controls.5 Similarly, a decrease in HRV was found in morbidly obese group compared with controls in 80 women, and significant associations between metabolic and hormonal factors and HRV measures disappeared after adjusting for body fat mass.5 It has also been suggested that HRV is reversible. In a handful of studies about change in ANS activity after weight loss in obese patients, an increase in HRV was noted after weight loss by gastroplasty,7 increased physical activity and calorie restriction,8-10 and anti-obesity medication.11

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Table 4. The Association between Adiposity Measure and Heart Rate Variability (HRV) Index in Multiple Linear Regression Model

|                      | Body mass index (1 SD=4.7 kg/m²) | % body fat mass (1 SD=4.7%) | Waist-to-hip ratio (1 SD=0.05) |
|----------------------|----------------------------------|-----------------------------|--------------------------------|
| In SDNN (ms)         |                                  |                             |                                |
| Crude                | -0.51 (0.01)*                    | -0.06 (0.01)*               | -0.13 (0.01)*                  |
| Age, sex-adjusted    | -0.04 (0.01)*                    | -0.04 (0.01)*               | -0.06 (0.02)*                  |
| Age, sex, CV-adjusted | -0.01 (0.01)                     | -0.02 (0.01)                | -0.03 (0.02)                   |
| In RMSSD (ms)        |                                  |                             |                                |
| Crude                | -0.15 (0.03)*                    | -0.18 (0.04)*               | -0.41 (0.04)*                  |
| Age, sex-adjusted    | -0.12 (0.03)*                    | -0.10 (0.03)*               | -0.18 (0.04)*                  |
| Age, sex, CV-adjusted | -0.07 (0.03)*                    | -0.06 (0.04)                | -0.12 (0.05)*                  |
| In LF (ms²)          |                                  |                             |                                |
| Crude                | -0.12 (0.03)*                    | -0.19 (0.04)*               | -0.33 (0.04)*                  |
| Age, sex-adjusted    | -0.09 (0.03)*                    | -0.13 (0.04)                | -0.15 (0.04)                   |
| Age, sex, CV-adjusted | -0.02 (0.04)                     | -0.08 (0.04)*               | -0.08 (0.05)                   |
| In HF (ms²)          |                                  |                             |                                |
| Crude                | -1.55 (0.37)*                    | -2.06 (0.42)*               | -3.32 (0.42)*                  |
| Age, sex-adjusted    | -1.27 (0.36)*                    | -1.56 (0.42)*               | -1.99 (0.49)*                  |
| Age, sex, CV-adjusted | -0.59 (0.40)                     | -0.93 (0.45)*               | -1.16 (0.54)*                  |
| pNN50 (%)            |                                  |                             |                                |
| Crude                |                                  |                             |                                |
| Age, sex-adjusted    | -0.32 (0.36)*                    | -0.42 (0.45)*               | -0.62 (0.54)*                  |
| Age, sex, CV-adjusted | -0.05 (0.03)                     | -0.03 (0.03)                | -0.03 (0.04)                   |
| LF/HF                |                                  |                             |                                |
| Crude                |                                  |                             |                                |
| Age, sex-adjusted    | -0.03 (0.03)                     | 0.02 (0.03)                 | -0.08 (0.03)*                  |
| Age, sex, CV-adjusted | -0.03 (0.03)                     | 0.03 (0.03)                 | -0.02 (0.04)                   |
|                      |                                  |                             |                                |
| ln, natural logarithm; SDNN, standard deviation of all normal RR intervals; RMSSD, root mean square of successive differences; LF, low frequency power; HF, high frequency power; pNN50, percentage of differences between adjacent RR intervals that are greater than 50 ms; LF/HF, ratio of the low/high frequency power; CV, cardiovascular.

Values are regression coefficient (standard error) for HRV measures with adiposity measures (per 1 standard deviation change) in multiple linear regression model.

*p<0.05.

CV included high blood pressure (<130/85 mm Hg vs. ≥130/85 mm Hg), fasting glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, and high sensitivity C-reactive protein.
male adolescents.25

The exact mechanisms linking increased abdominal adiposity with low HRV are unclear. A plausible explanation for the association involves compartment-specific alterations in the balance of sympathetic/parasympathetic outflow. Increased parasympathetic dominance in the visceral compartment and increased sympathetic tone in the thoracic and movement compartments could contribute to the metabolic syndrome, including visceral fat accumulation.24,26

Several limitations in the present study should be considered. First, the study sample consisted of a relatively small number of obese participants, which might have led to an underestimation of the associations between adiposity and HRV measures. Second, this study had a cross-sectional design, which does not allow for an evaluation of temporal relationships. Third, HRV has been known to be very vulnerable to diurnal, postural, and emotional changes. Therefore, it is necessary to carefully adjust the data acquiring conditions to get valid HRV, though it is as short as 5 minutes. In the current study, we obtained stationary HRV by keeping the following conditions: recording ECG in the morning to be free from diurnal change; keeping supine position to make effects of posture change small; and selecting stationary 5-min segment from 10-min HRV to avoid nonstationarity. However, we might not have completely controlled conditions related to HRV such as psychological status, acute illness, and medications that could influence HRV measurements. Fourth, as we conducted this study using stationary 5-minute segment from 10-minute HRV, the current results might not extend to the findings that were derived from long-term HRV extracted from 24-hour ECG that gives some important information about long-term variability and fluctuation. However, it is not easy to acquire long-term ECG/HRV from a large population of more than 1000 subjects. Also, there has been sufficient evidence to support that this short-duration stationary HRV can reflect cardiac ANS function.18 Finally, despite adjustment for potential confounders, residual and unmeasured confounders may affect the results.

In conclusion, our data confirm an association between increased adiposity and low HRV. However, we found that the strength of association is not uniform; it is rather specific to different adiposity measures and weight subgroups. WHR and PBF are better indicators of low HRV than BMI. In addition, our data provide evidence that, irrespective of age, gender, and CV risk factors, these associations were consistent and stronger in overweight subgroup. These findings support clinical importance of abdominal obesity
as a risk factor for CV disease.

ACKNOWLEDGEMENTS

This study was supported by the Korean Ministry of Knowledge Economy (10033321), and in part to Dong-Gu Shin by the 2004 Yeuungnam University Medical Center Research Grant.

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