

심박변이도 측정상 자율신경계 이상을 보이는 경우 대사 및 심혈관질환 위험인자들의 위험도

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Risk of Metabolic and Cardiovascular Risk Factors in Individuals with Autonomic Imbalance Measured by Heart Rate Variability

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Background: Studies have reported that reduced autonomic nervous system activity could result in a sub-optimal health condition and various diseases, further increasing the mortality rate. The present study aimed to determine the difference in risk factors for metabolic and cardiovascular diseases in patients with reduced or unstable autonomic activity according to heart rate variability test results.

Methods: We recorded blood pressure, physical measurements (body mass index and waist circumference), fasting blood glucose, and blood lipid status. Indicators representative of autonomic nerve functionality (total power [TP], standard deviation of the normal-to-normal intervals [SDNN], low-frequency band [LF], high-frequency band [HF]) were measured using a 5-minute heart rate variability test. Each indicator was divided into quartiles.

Results: In men, the risk of abdominal obesity was high in the group with a low TP. In the group with a low SDNN, TP, and LF, the risk of a blood pressure increase was high. When LH and HF were low, there was a high risk of increased fasting blood sugar, whereas when LH was low, there was a high risk of hypertriglyceridemia. Women with SDNN loss had higher odds ratios for abdominal obesity and low high-density lipoprotein cholesterolemia. **Conclusions:** These results indicate a higher risk of having risk factors for metabolic and cardiovascular diseases, such as abdominal obesity, elevated blood pressure, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein cholesterolemia in a group with reduced autonomic activity measured by heart rate variability. Women with a low SDNN had a 4.51-fold higher risk of abdominal obesity than women with a high SDNN, showing the greatest value of the heart rate variability indices.

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INTRODUCTION

Heart rate variability (HRV) refers to minute variations in heartbeat cycles. Cardiac impulses are influenced by the autonomic nervous system (ANS), which refers to the interaction between the sympathetic and parasympathetic nervous systems, and minute variations in the heart rate are caused by the interaction between the internal and external

environment. Accordingly, the activity and balance of the ANS can be noninvasively determined by analyzing the HRV.¹⁾

The ANS is known to play a fundamental role in human health and disease. Healthy people constantly change and adapt themselves to various environments because of their adequate ANS activity. Conversely, in those individuals with poor ANS activity, various diseases can occur due to reduced internal adaptability to the environment. Accordingly, previous studies have analyzed HRV, which can indicate the level of ANS activity, and found that reduced HRV is associated with poor health, various diseases, and increased mortality rate.²⁻⁵⁾

Death rates have been found to increase when HRV is low regardless of the cause of death, and this risk increases when patients with cardiovascular disease present risk factors such as hypertension and diabetes.⁴⁻⁶⁾ The risk of death due to cardiovascular diseases also increased in the absence of other underlying diseases when HRV was low, and this risk was even higher in diabetic patients. Furthermore, low HRV itself has been associated with various metabolic and cardiovascular risk factors.^{7,8)} In this regard, several hypotheses have been proposed explaining that such psychosocial problems can reduce HRV by the same mechanism, ultimately causing diseases.

This study aimed to identify the types of autonomic imbalances in a mono-ethnic South Korean population with low HRV by examining differences in the risk factors of metabolic and cardiovascular diseases regarding each HRV index. In particular, as previous studies have mainly examined the relationship between high levels of low-density lipoprotein (LDL) cholesterol^{9,10)} and serum lipids among the metabolic indices, the present study investigated the association between high levels of triglyceride and low levels of high-density lipoprotein (HDL) cholesterol.

METHODS

The study was approved by the Institutional Review Board of Jeju National University Hospital, Jeju, Republic of Korea (IRB No. JEJUNUH 2016-01-001). This study was exempted from the obligation to submit the study consent of the subjects because of the very low risk to health of the study subjects due to the retrospective medical records analysis method by the Institutional Review Board of

Jeju National University Hospital. In this regard, participants who had a health examination performed at Jeju National University Hospital received on the day of examination a form notifying them that their examination results, excluding personal information, would be used for research purposes.

1. Study subjects

A retrospective review was conducted using the medical records of individuals whose HRV was measured when they underwent anthropometry, electrocardiogram, and blood tests during health examinations between August 2009 and December 2015. During the health examination, a survey was conducted in which participants were asked whether they were diagnosed with and taking medication for hypertension, diabetes, dyslipidemia, and heartbeat irregularities. Those with arrhythmias, such as atrial fibrillation, atrial flutter, atrioventricular block, heart rate <50 bpm or ≥100 bpm, and those previously diagnosed with and currently taking medication for heartbeat irregularities were excluded.

2. Measurement of HRV

HRV was measured with a fingertip pulse wave sensor (BFM-5000P; Medcore Co., Ltd., Seoul, Korea) while participants were in a sitting position without speaking or moving, unless necessary, in a small room. The heart rate was recorded for 5 minutes and the following time-domain measures of HRV were determined: standard deviation of the normal-to-normal intervals (SDNN) and in review frequency-domain variables of HRV, including total power (TP) (0.0-0.4 Hz), high frequency (HF) band (0.15-0.40 Hz), and low frequency (LF) band (0.04-0.15 Hz). Subjects were grouped by quartiles of HRV indices: SDNNs, and 5-minute TP, LF, and HF.

3. Metabolic and cardiovascular risk factors

In this study, the risk factors of metabolic and cardiovascular disorders were analyzed including abdominal obesity, blood pressure elevation, blood glucose elevation, hypertriglyceridemia, and low HDL cholesterolemia. The criteria for abdominal obesity was defined according to the Korean Society for the Study of Obesity¹¹⁾ and, in this re-

gard, having a waist circumference of ≥ 90 cm and ≥ 85 cm in male and female participants, respectively, was considered as abdominal obesity. Blood pressure elevation (high BP) was defined as blood pressure level ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic, or a diagnosis of hypertension and currently taking antihypertensive medication. Blood glucose elevation (high FPG) was defined as fasting (≥ 12 hours) blood glucose level ≥ 100 mg/dL or a diagnosis of diabetes and currently taking medication. Hypertriglyceridemia (high TG) was defined as fasting (≥ 12 hours) triglyceride level ≥ 150 mg/dL or a diagnosis of dyslipidemia and currently taking medication. Low HDL cholesterolemia (low HDL) was defined as fasting (≥ 12 hours) HDL cholesterol level < 40 mg/dL for men and < 50 mg/dL for women.

4. Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). *P*-values less than 0.05 were considered statistically significant. Regarding the comparison of gender differences in baseline characteristics, age differences were analyzed by *t*-test and the other variables were age-adjusted using analysis of covariance (ANCOVA). Correlations between HRV parameters and cardiovascular risk factors were analyzed using age-adjusted partial correlation. We compared the prevalence rate of each metabolic and cardiovascular risk factor per quartile group

of HRV variables. The odds ratio (OR) and 95% confidence interval (CI) for each metabolic and cardiovascular risk factor per quartile of HRV variables were calculated using logistic regression analysis.

RESULTS

1. Baseline characteristics of the study group

Finally, the total number of participants was 702 (530 men and 172 women). The average age of male participants was 42.8 ± 11.1 years, which was higher than that of female participants (38.9 ± 11.9 years, $t=3.913$, $P<0.001$ by *t*-test). Differences in anthropometric indices, blood pressure, fasting blood glucose, and serum lipids between male and female participants are presented in Table 1. Men had higher body mass index, waist circumference, blood pressure, triglyceride and fasting blood sugar, but lower HDL cholesterol than women (all $P<0.001$ by ANCOVA after adjustment for age).

The number of male and female participants with abdominal obesity (waist circumferences for men and women of > 90 cm and > 85 cm, respectively) was 166 (31.3%) and 29 (16.9%). The total number of male and female participants who met the criteria for blood pressure elevation was 275 (51.9%) and 27 (15.7%), respectively. The total number of male and female participants who met the criteria for elevated

Table 1. Baseline characteristics of the study group

	Men (n=530)	Women (n=172)	<i>F</i>	<i>P</i> of difference
BMI, kg/m ²	25.5 \pm 3.2	22.9 \pm 3.5	73.32	<0.001
WC, cm	86.41 \pm 8.05	76.60 \pm 8.99	167.51	<0.001
SBP, mmHg	127.6 \pm 13.0	114.6 \pm 12.30	120.94	<0.001
DBP, mmHg	80.1 \pm 10.2	71.2 \pm 9.50	89.65	<0.001
TG, mg/dL	138.8 \pm 84.1	82.9 \pm 44.6	66.94	<0.001
HDL-cholesterol, mg/dL	48.4 \pm 10.9	57.9 \pm 12.3	94.44	<0.001
FPG, mg/dL	94.6 \pm 17.0	87.8 \pm 12.1	16.06	<0.001
SDNN, ms	43.49 \pm 19.28	41.89 \pm 19.29	3.37	0.067
TP, ms ²	1,567.45 \pm 1,784.79	1,339.62 \pm 1,278.95	5.78	0.016
LF, ms ²	464.32 \pm 544.15	322.97 \pm 410.49	17.98	<0.001
HF, ms ²	277.01 \pm 382.74	292.65 \pm 351.07	0.15	0.695

Values are presented as mean \pm standard deviation. *P* values were derived by analysis of covariance (age-adjusted). Degrees of freedom: *F* (1, 699).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HF, high frequency; LF, low frequency; SBP, systolic blood pressure; SDNN, standard deviation of the normal-to-normal intervals; TG, triglyceride; TP, total power; WC, waist circumference.

blood glucose was 121 (22.8%) and 12 (7.0%), respectively. The total number of male and female participants with hypertriglyceridemia was 184 (34.7%) and 14 (8.1%), respectively, and the number of male and female participants with low HDL cholesterolemia was 122 (23.0%) and 46 (26.7%), respectively. Among women, the proportion of elevated blood glucose and hypertriglyceridemia was less than 10%, which was relatively low. Therefore, there was a limitation in analyzing the difference in the OR of elevated blood glucose and hypertriglyceridemia in women with low HRV level compared to those of other groups.

2. Baseline characteristics of HRV parameters in the study group

In terms of gender and age, there were statistically significant inverse correlations between all HRV indices (SDNN, TP, LH, and HF) for men as age increased ($r=-0.248$, -0.193 , -0.226 , and -0.239 ; all $P<0.001$). Similarly, all HRV indices of female participants showed inverse correlations with increase in age, but statistical significant differences were found only for TP ($r=-0.297$, $P<0.001$), LH ($r=-0.400$, $P<0.001$), and HF ($r=-0.164$, $P=0.031$) indices. The correlation with SDNN was not statistically significant ($r=-0.145$, $P=0.058$). A gender-based comparison of HRV indices after controlling for age revealed significant decreases in TP ($P=0.016$) and LF ($P<0.001$) indices in female participants

Table 2. Comparison of the OR of metabolic abnormality in the lowest HRV quartile group (highest group set to OR, 1.0)

	Men		Women	
	OR	<i>P</i>	OR	<i>P</i>
SDNN				
Abdominal obesity	1.47 (0.87-2.51)	0.154	4.51 (1.15-17.72)	0.031
High BP	1.77 (1.06-2.94)	0.029	3.78 (0.95-15.03)	0.059
High TG	1.49 (0.87-2.54)	0.149	-	-
Low HDL	1.16 (0.65-2.09)	0.610	3.01 (1.08-8.33)	0.034
High FPG	1.55 (0.83-2.88)	0.169	1.29 (0.21-7.90)	0.784
TP				
Abdominal obesity	1.83 (1.06-3.17)	0.031	3.83 (0.94-15.57)	0.060
High BP	1.74 (1.05-2.88)	0.033	4.42 (0.86-22.68)	0.075
High TG	1.32 (0.78-2.23)	0.301	-	-
Low HDL	0.88 (0.49-1.57)	0.666	2.68 (0.90-7.92)	0.075
High FPG	1.44 (0.79-2.63)	0.231	-	-
LF				
Abdominal obesity	1.76 (0.99-3.13)	0.054	1.50 (0.35-6.42)	0.583
High BP	1.82 (1.07-3.11)	0.027	1.92 (0.36-10.32)	0.445
High TG	1.82 (1.04-3.18)	0.036	-	-
Low HDL	1.52 (0.82-2.81)	0.181	1.96 (0.55-7.08)	0.302
High FPG	2.01 (1.05-3.85)	0.036	0.47 (0.04-5.77)	0.556
HF				
Abdominal obesity	1.13 (0.67-1.92)	0.648	2.30 (0.70-1.09)	0.172
High BP	1.07 (0.65-1.75)	0.799	2.26 (0.57-8.92)	0.243
High TG	1.51 (0.89-2.54)	0.127	-	-
Low HDL	0.80 (0.44-2.45)	0.464	2.20 (0.78-6.19)	0.135
High FPG	2.30 (1.21-4.38)	0.011	0.58 (0.03-11.12)	0.718

P values were derived by logistic regression analysis.

Abbreviations: BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HF, high frequency; LF, low frequency; OR, odds ratio; SDNN, standard deviation of the normal-to-normal intervals; TG, triglyceride; TP, total power.

compared to male participants. However, there were no statistically significant gender differences for SDNN ($P=0.067$) and HF ($P=0.695$), as shown in Table 1.

3. OR of metabolic abnormality among the groups with the lowest and highest HRV indices

Table 2 shows the comparison of the relative risks of metabolic and cardiovascular diseases by each risk factor for the groups with the lowest and highest HRV indices. Each HRV index was categorized into quartiles. Regarding abdominal obesity, the risk of morbidity was significantly increased for women in the lowest SDNN group (OR, 4.51; 95% CI, 1.15-17.72) and for men in the lowest TP group (OR, 1.83; 95% CI, 1.06-3.17). The prevalence of high BP was significantly increased for men in the lowest SDNN (OR, 1.77; 95% CI, 1.06-2.94), TP (OR, 1.74; 95% CI, 1.05-2.88), and LF (OR, 1.82; 95% CI, 1.07-3.11) groups. High FPG morbidity was significantly increased for men in the lowest LF (OR, 2.01; 95% CI, 1.05-3.85) and HF (OR, 2.30; 95% CI, 1.21-4.38) groups, although no relationship with decreased HRV was found in women. The prevalence of high TG was significantly increased for men in the lowest LF group (OR, 1.82; 95% CI, 1.04-3.18) but not in men with other HRV indicators or in women. Low HDL significantly was increased only for women in the lowest SDNN group (OR, 3.01; 95% CI, 1.08-8.33).

DISCUSSION

The results of this study revealed significant increases in the risk of metabolic and cardiovascular diseases with decreases in HRV indices. These findings can be considered to be an extension of previous studies' results,^{2-6,7)} which have identified a relationship between HRV reduction and cardiovascular diseases.

Specifically, results showed that the risk of contracted abdominal obesity in female participants with low SDNN was 4.51 times higher than that of female participants with high SDNN, while the risk of contracted abdominal obesity in male participants was 1.83 times higher when TP was low. Previous studies have also found that HRV in obese women is lower than in normal-weight women.¹²⁾ However, after losing weight, the reduced HRV of these women was recovered.¹³⁾ This indicates that the findings of the present study are an

extension of research that has studied the relationship between obesity and HRV reduction. Nevertheless, the present study found differences in specific indices. Previous studies have indicated decreases in TP or HF in obese women, however, in the present study, no statistically significant increase in the risk of abdominal obesity was found in those individuals with low TP and HF. Although some differences were identified, variations in HRV were only found with decreases in TP and SDNN for men and women, respectively.

In this study, the risk of blood glucose elevation significantly increased only in men with low LF and HF. Previous studies have also reported significantly lower HRV in patients with diabetes than in people without this health condition, and even in the absence of diabetes, HF or LF was significantly negatively correlated with fasting blood glucose and fasting insulin.^{14,15)}

Furthermore, results revealed that the risk of elevated blood pressure significantly increased in male participants with reduced SDNN, TP, and LF, but not in those who presented reduced HF. However, the nonsignificant association of elevated blood pressure with HF found in the present study is not in line with the results of previous studies, which have reported reduced HF in patients with high blood pressure compared to other groups, as well as a higher risk of future hypertension with reduced HF.¹⁶⁾ Nevertheless, the present findings are consistent with those of a previous study,²⁾ which reported a significant relationship between low LF and incidence of hypertension only in men. Another study³⁾ reported that the risk of developing hypertension in the future was high when SNDD decreased even when various accompanying risk factors were corrected. This finding is similar to that of the present study, in which the risk of blood pressure elevation morbidity was 1.77 times higher in the low SDNN group compared to other groups.

Additionally, the present study found that the risk of hypertriglyceridemia was higher in men with low LF and, for women, the risk of low HDL cholesterolemia was high when SDNN was low. Research concerning the relationship between HRV and triglyceride or HDL cholesterol is insufficient, but inverse correlations have been found in some studies related to LDL cholesterol, where higher increases in LDL cholesterol were associated with lower SDNN and RMSSD.⁹⁾

The correlation analysis of age and HRV in this study revealed inverse correlations for both genders in most of the

coefficients between HRV indices and age, except for SDNN in female participants. A previous study¹⁷⁾ also reported low HRV as age increased. Furthermore, lower HF was observed in participants with a family history of hypertension compared to participants without this type of history.¹⁸⁾ In this regard, TP and HF were lower in participants with a family history of diabetes than in participants without such history.¹⁹⁾

Reductions in HRV can be considered as an indication of a decrease in the vagus nerve activity due to autonomic imbalance. Such changes are related to a greater incidence of cardiovascular diseases and death rates. Increases in various inflammatory response levels when HRV decreases^{20,21)} indicate that lower HRV can deteriorate health.

Chronic pain diseases such as fibromyalgia, irritable bowel syndrome, and functional gastrointestinal disorders, whose underlying mechanisms have been difficult to determine, have been recently explained by the polyvagal theory²²⁾ as generated by an unstable ANS and, in this regard, reduced HRV has been reported in these patients. Smoking can reduce vagal activity and immediate reduction in the average HF has been observed after smoking only one cigarette.²³⁾ Besides, smoking in pregnant women has been reported to reduce HRV in neonates.²⁴⁾ On the other hand, significantly lower SDNN, LF, and HF have been observed in individuals with insufficient exercise compared to those who regularly exercise.²⁵⁾

Lifestyle risk factors can be addressed, and increases in HRV have been observed through behavioral changes, such as smoking cessation, weight loss, and increased exercise. In particular, improvement in vagal activity has been observed after smoking cessation for 24 hours, 1 week, and 8 weeks.²⁶⁻²⁸⁾ Regarding exercise, regular aerobic exercise for 12 weeks was reported to increase SDNN and HF.²⁹⁾ With regards to obesity, significant increases in SDNN and HF were observed 1 year after bariatric surgery in participants who were obese and had lower SDNN compared to normal participants.¹²⁾ Recent studies have also shown that HRV can be improved using neuroscience equipment.³⁰⁾ This type of equipment has demonstrated to be effective in improving physical symptoms caused by ANS instability such as postmenopausal flushing³¹⁾ and post-traumatic stress disorder.³²⁾

The HRV test is a non-invasive method that can be easily administered by being comfortably seated in a quiet room for 5 minutes. Accordingly, careful attention should be paid to the existence of comorbidity revealed through HRV tests,

because the threat of risk factors discussed above is higher when HRV decreases. In this regard, it could be a good educational practice to encourage patients to constantly improve their lifestyle habits, because HRV can be easily recovered by changing these habits.

High-risk factors of metabolic and cardiovascular diseases can increase death rates. This can happen specifically if the HRV is low in individuals who present the risk factors mentioned above. In this case, the risk of developing cardiovascular diseases as well as death rates due to these causes can increase. Since many studies have reported the effectiveness of smoking cessation, increased exercise, and weight loss, more thorough education is needed for people whose lifestyle habits need to be modified, and HRV can be used to monitor the results of applying these educational strategies.

However, this study has a limitation in reflecting the current status because the study data collection period has been protracted, and it has a limitation in that it was not amenable to allowing investigation of other factors such as lifestyle, which can affect HRV and cardiovascular risk factors. Therefore, additional research including recent research data and lifestyle conditions that can affect various metabolic and cardiovascular diseases will be needed.

In conclusion, results from this study with South Korean participants revealed that lower HRV in men was associated with a higher risk of abdominal obesity, blood pressure elevation, blood glucose elevation, and hypertriglyceridemia. On the other hand, lower HRV in women was related to a risk of increased low HDL cholesterolemia. In particular, the risk of abdominal obesity in women was 4.51 times higher with low SDNN.

요 약

연구배경: 심박변이도는 자율신경계의 활성도를 측정하는 비침습적 방법으로 알려져 있다. 심박변이도 검사를 통해 자율신경계 활성도가 저하되어 있는 경우에는 건강 상태가 좋지 않고, 다양한 질환을 가지고 있으며 더 나아가 사망률을 높인다는 연구 보고들이 있다. 본 연구는 심박변이도 검사를 통해 측정한 자율신경 상태가 감소되거나 불안정한 경우 대사질환 및 심혈관질환의 위험인자를 보유할 위험도가 어떻게 차이가 나는지를 확인해 보고자 하였다.

방법: 신체계측 검사를 통해 비만도 및 수축기와 이완기 혈압을 측정하였고, 혈액 검사를 통해 공복혈당, 혈중지질 상태를 검사하였다. 5분간의 심박변이도 검사를 통해 자율

신경 상태를 대변하는 standard deviation of NN intervals (SDNN), 5-minute total power (TP), low frequency (LF), high frequency (HF)를 각각 측정하였다. 심박변이도 각 지표들을 사분위로 나누어 높은 수치를 보이는 경우를 기준으로 하였을 때 가장 낮은 그룹에서 비만, 혈압 상승, 공복혈당 이상, 이상지질혈증 등을 동반한 위험도에 어떠한 차이가 있는지를 확인하였다.

결과: 남자의 경우 TP가 낮은 그룹에서 복부비만 위험도가 높았으며, SDNN, TP, LF가 낮은 그룹에서는 혈압 상승 위험도가 높았다. LH와 HF가 낮은 경우는 공복혈당 상승, 그리고 LH가 낮은 경우에는 고중성지방혈증에 이환될 위험도가 높았다. 여성은 SDNN이 낮은 경우 복부비만과 낮은 고밀도콜레스테롤혈증에 이환될 위험도가 높았다.

결론: 본 연구 결과 심박변이도로 측정된 모든 지표들에서 자율신경 활성도 감소 및 불안정성이 있는 군에서 그렇지 않은 군과 비교하였을 때 유의하게 복부비만, 혈압 상승, 혈당 상승, 고중성지방혈증 및 낮은 고밀도콜레스테롤혈증 등 대사질환 및 심혈관질환의 위험인자를 보유할 위험도가 높았다. 특히 여성의 경우 낮은 SDNN 그룹에서 복부비만에 이환될 위험도가 4.51배였다.

중심 단어: 심박변이도, 대사질환, 심혈관질환, 자율신경계

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