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Determinants for Heart Rate Variability in a Normal Korean Population

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Received: 24 February 2011
Accepted: 29 August 2011

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This study examined the normal ranges and the determinants for various parameters of the short-term heart rate variability (HRV) measurements in a large Korean sample of healthy people. HRV measurements were obtained in 2,748 healthy men and 735 healthy women 18-65 yr of age. The mean total power (TP), low frequency (LF), high frequency (HF), and LF/HF ratio were $1,358.9 \pm 1,840.8$ ms^2, 417.3 ± 807.6 ms^2, 254.1 ± 414.1 ms^2, and 2.4 ± 20.9 ms^2 in the frequency-domain spectral analysis. The mean standard deviation of the normal-to-normal (NN) interval (SDNN) and the square root of the mean squared differences of successive NN intervals (RMSSD) were 39.6 ± 22.1 ms and 29.7 ± 18.1 ms in the time-domain analysis. The female subjects had significantly higher SDNN, RMSSD, and HF values than the male subjects. After controlling for age, there was no statistically significant difference in the SDNN. Quantile regression analysis showed that age and mean heart rate had a significant impact on short-term HRV measurement. Given that both clinicians and researchers are increasingly relying on short-term HRV assessment in measuring stress, our work suggests that age and gender should be considered as independent determinants for HRV.

Key Words: Age; Gender; Heart Rate Variability; Autonomic Nervous System; Psychophysiology

INTRODUCTION

Heart rate variability (HRV) provide a perspective on both sympathetic and parasympathetic nervous system functioning (1). HRV, which is defined as 'the amount of fluctuations from the mean heart rate', is primarily controlled by the continuous interplay of the autonomic nervous system (ANS). Two frequency components are usually distinguishable in short-term HRV: high frequency (HF) and low frequency (LF) components (2).

The number of patients visiting health-promotion centers and primary practitioners for the assessment and treatment of stress symptoms is increasing in Korea. Therefore, many hospitals and health-promotion centers measure both psychological stress and ANS function at the initial work-up and routine medical checkups to apply these pieces of information to patient care. Recently, there has been growing interest in HRV because several studies have consistently shown an association between reduced HRV and increased risk of cardiovascular morbidity and mortality (3-6), poor prognosis of many other diseases (7-9), and an association between HRV and mental disorders (10).

To apply HRV measures in monitoring physiological stress levels in clinical practice or medical checkups, normative values of HRV variables and their determinants are required. Until now, there have been a few studies on normative data of HRV

in a normal population without cardiac diseases (5); one study involved standardized tests of HRV for autonomic function testing in healthy Koreans (11), but it had a limit by its relatively small sample size. A study with a larger sample size has the advantage of enabling control of other sources of variance, such as age, obesity and health-related habits.

In this study, we evaluated the normal ranges of various parameters of short-term HRV in a large Korean sample of healthy people to obtain normative data on HRV. We also analyzed the impact of gender, age, and other relevant demographic and clinical variables on short-term HRV measurements.

MATERIALS AND METHODS

Subjects

We recruited 2,748 men and 735 women who were 18-65 yr of age, from 5 health-promotion centers in Korea during their annual medical check-up. Recruitment of subject was conducted from April 1, 2003, to August 31, 2003. All participants were screened for medications and medical conditions. Psychiatric diagnoses were assessed using the Mini-International-Neuropsychiatric Interview (M.I.N.I.) (12) by an experienced psychiatric nurse and a psychiatrist. Thirty-nine participants with histories of major medical disorders and seven participants with

histories of major psychiatric disorders were excluded. Before the HRV measurements, the participants answered a questionnaire on personal information and their life habits (e.g., smoking, alcohol consumption, coffee drinking, and exercise). After the measurement, 41 participants, who had an abnormally high standard deviation (SD) of the normal-to-normal interval (SDNN) in the HRV (≥ 100, 3 standard deviations), were excluded from the analysis. Finally 2,679 men and 717 women who completed the HRV measurements and questionnaires were included in the analysis.

Measurement of HRV

All subjects were instructed to avoid alcohol or caffeinated beverages after 10 p.m. (22:00) on the night before the HRV measurements. In addition, they refrained from smoking 1 hr before the measurements. To control for diurnal variation, HRV was measured between 8 a.m. (08:00) and 12 a.m. (12:00) by using the SA-2000E model (Medi-core, Seoul, Korea). Each subject was comfortably seated on a chair, electrodes were placed on their wrists and left foot to derive HRV for 5 min, and the subject was guided to breathe according to their usual rate during the HRV measurement.

The following HRV parameters were measured by frequency domain spectral analysis (13): total power (TP), LF, and HF. TP is the variance of the normal-to-normal interval (NN) over a temporal segment. The LF/HF ratio was calculated because it considered to reflect sympatho-vagal balance or sympathetic modulation (2). The standard deviation of the normal-to-normal interval (SDNN) was used to estimate long-term components of the HRV. It is calculated by statistical time domain measurements. The square root of the mean squared differences of successive NN intervals (RMSSD) was also calculated by statistical time domain measurements.

Statistical analysis

All HRV variables were expressed as the mean ± SD and were tested by the Kolmogorov-Smirnov test for normal distribution. All HRV variables were then compared between age-matched groups. ANOVA was used to compare age and life habits with the HRV variables. Quantile regression models were constructed to identify the association between dependent variables (SDNN, RMSSD, TP) and the independent variables (mean heart rate, age, body mass index [BMI], and systolic blood pressure) analyzed. This models enable the effect of independent variables on different points of the distribution of the dependent variables which were asymmetric. All HRV variables were described as percentiles. The quantiles were based on the distribution of HRV values where the 10th, 25th, 50th, 75th, and 90th percentiles were considered, and the median is the 50th quantile. All statistical analyses were performed by using the SPSS 12.0 for Windows (SPSS Korea Datasolution Inc.).

Ethics statement

All participants provided informed consent after receiving a complete explanation regarding the study.

RESULTS

The mean age of the subjects was 41.4 ± 9.00 yr (range, 18-65 yr); the male and female subjects had mean ages of 42.3 ± 8.3 and 38.0 ± 10.5 yr, respectively. Educationally, subjects who were high school graduates and had higher qualifications were 3,022 (89%). Smokers were 1,956 (57.6%) and subjects who reported drinking alcohol more than once a week were 1,681 (49.5%). Subjects who reported exercising more than once a week were 2,211 (65.1%), and subjects who consumed coffee regularly were 2,649 (78.0%). Their demographic characteristics are presented in Table 1.

The mean TP, LF, HF, and LF/HF ratio were 1,358.9 ± 1,840.8 ms^2, 417.3 ± 807.6 ms^2, 254.1 ± 414.1 ms^2, and 2.4 ± 20.9, respectively, in the frequency-domain spectral analysis. The mean SDNN and RMSSD were 39.6 ± 22.1 ms and 29.7 ± 18.1 ms, respectively, in the time-domain analysis. The results of the 5-min HRV resting measurements in the normal population are presented in Table 2. In men, the SDNN, RMSSD, TP, LF, and HF significantly decreased with increasing age ($F = 42.66$, $P < 0.001$; $F = 30.23$, $P < 0.001$; $F = 24.60$, $P < 0.001$; $F = 16.36$, $P < 0.001$; $F = 23.13$, $P < 0.001$, respectively), as shown in Table 3. In female, the SDNN and RMSSD significantly decreased with increasing age ($F = 8.52$, $P < 0.001$; $F = 4.19$, $P = 0.006$) as shown in Table 4.

The female subjects had significantly higher SDNN, RMSSD, and HF values than the male subjects ($F = 4.74$, $P = 0.030$; $F = 19.09$, $P < 0.001$; $F = 26.09$, $P < 0.001$, respectively). After controlling for age, there was no statistically significant difference in the SDNN. However, the RMSSD, LF/HF ratio, logarithmic (Ln) TP, Ln LF, and Ln HF were significantly different between genders ($F = 4.38$, $P = 0.037$; $F = 40.59$, $P < 0.001$; $F = 3.86$, $P = 0.005$; $F = 27.19$, $P < 0.001$; and $F = 6.78$, $P = 0.009$, respectively).

There were no significant differences in the HRV variables between the smokers and the non-smokers. However, the SDNN, RMSSD and HF of the participants who drank alcohol more than once a week were lower than those of the participants who drank less than once a week ($F = 3.74$, $P = 0.053$; $F = 3.92$, $P = 0.048$; $F = 3.40$, $P = 0.065$, respectively). The Ln TP, Ln LF and Ln HF

Table 1. The demographic characteristics of participants

Age (yr)	Men No. (%)	Women No. (%)	Total No. (%)	χ²	P value
≤ 29	168 (5.0)	186 (5.5)	354 (10.4)	251.84	< 0.001
30-39	805 (23.7)	222 (6.5)	1,027 (30.2)		
40-49	1,185 (34.9)	203 (6.0)	1,388 (40.9)		
50 ≤	521 (15.3)	106 (3.1)	627 (18.5)		
Total	2,679 (78.9)	717 (21.1)	3,396 (100.0)		

values were significantly higher in the participants who consumed coffee regularly than in those did not ($F = 6.55$, $P = 0.011$; $F = 4.78$, $P = 0.029$; $F = 4.49$, $P = 0.034$). Regarding exercise, the SDNN, RMSSD, TP, LF, and HF values were significantly increased with the exercise frequency ($F = 8.47$, $P < 0.001$; $F = 13.42$, $P <$ 0.001; $F = 4.97$, $P = 0.002$; $F = 4.14$, $P = 0.006$; and $F = 4.70$, $P = 0.003$, respectively).

Quantile regression analysis identified several HRV parameters that were significantly associated with other demographic or clinical variables. Age and mean heart rate seemed to be the

Table 2. The results of the 5-minutes HRV resting measures in a normal population

Variables	No.	Mean ± SD	KS	P value	Percentile				
					10th	25th	50th	75th	90th
SDNN (ms)	3,408	39.6 ± 22.1	0.135	< 0.01	22.2	28.2	36.4	46.3	58.1
RMSSD (ms)	3,408	29.7 ± 18.1	0.122	< 0.01	13.5	18.8	25.8	35.8	47.9
TP (ms^2)	3,403	1,358.9 ± 1,840.8	0.240	< 0.01	347.0	558.3	934.3	1,578.0	2,523.9
VLF (ms^2)	3,405	688.0 ± 1,043.7	0.263	< 0.01	142.4	241.4	446.2	802.0	1,372.8
LF (ms^2)	3,407	417.3 ± 807.6	0.305	< 0.01	74.5	132.6	248.8	451.4	799.4
HF (ms^2)	3,407	254.1 ± 414.1	0.271	< 0.01	38.2	75.1	149.4	287.9	528.5
LF/HF	3,407	2.4 ± 20.9	0.454	< 0.01	0.6	0.9	1.7	3.1	5.1
Ln TP	3,085	6.8 ± 0.8	0.041	< 0.01	5.9	6.3	6.8	7.4	7.8
Ln VLF	3,085	6.1 ± 0.9	0.029	< 0.01	5.0	5.5	6.1	6.7	7.2
Ln LF	3,085	5.5 ± 1.0	0.041	< 0.01	4.3	4.9	5.5	6.1	6.7
Ln HF	3,085	5.0 ± 1.1	0.049	< 0.01	3.7	4.3	5.0	5.7	6.2

SD, standard deviation; KS, Kolmogorov-Smirnov test; SDNN, Standard deviation of normal-to-normal interval; RMSSD, the square root of the mean squared differences of successive NN intervals; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; Ln, Logarithmic.

Table 3. The differences of HRV variables in men by age group

Variables	Mean ± SD in age group (yr)				F	P value
	≤ 29	30-39	40-49	50 ≤		
SDNN (n = 2,671)	51.88 ± 57.27 (n = 168)	42.47 ± 16.68 (n = 804)	38.00 ± 17.60 (n = 1,181)	32.57 ± 14.91 (n = 518)	42.66	< 0.001
RMSSD (n = 2,671)	36.10 ± 19.18 (n = 168)	31.82 ± 16.73 (n = 804)	28.22 ± 17.89 (n = 1,181)	23.21 ± 16.66 (n = 518)	30.23	< 0.001
TP (n = 2,666)	1,973.01 ± 1,723.13 (n = 166)	1,539.39 ± 1,662.35 (n = 801)	1,280.56 ± 1,761.80 (n = 1,181)	922.85 ± 1,059.32 (n = 518)	24.60	< 0.001
LF (n = 2,670)	704.16 ± 847.26 (n = 167)	499.67 ± 751.59 (n = 804)	400.31 ± 947.10 (n = 1,181)	258.54 ± 513.67 (n = 518)	16.36	< 0.001
HF (n = 2,670)	393.36 ± 462.84 (n = 167)	277.88 ± 341.92 (n = 804)	219.76 ± 364.33 (n = 1,181)	160.08 ± 321.99 (n = 518)	23.13	< 0.001
LF/HF (n = 2,670)	3.16 ± 6.71 (n = 167)	2.74 ± 2.69 (n = 804)	2.65 ± 3.21 (n = 1,181)	2.58 ± 3.22 (n = 518)	1.36	0.253

SD, standard deviation; SDNN, Standard deviation of normal-to-normal interval; RMSSD, The square root of the mean squared differences of successive NN intervals; TP, total power; LF, low frequency; HF, high frequency.

Table 4. The differences of HRV variables in women by age group

Variables	Mean ± SD in age group (yr)				F	P value
	≤ 29	30-39	40-49	50 ≤		
SDNN (n = 712)	44.36 ± 14.96 (n = 183)	44.70 ± 27.76 (n = 222)	37.80 ± 15.60 (n = 202)	34.21 ± 26.40 (n = 105)	8.52	< 0.001
RMSSD (n = 712)	33.88 ± 15.57 (n = 183)	34.79 ± 19.24 (n = 222)	30.42 ± 18.19 (n = 202)	27.70 ± 27.07 (n = 105)	4.19	0.006
TP (n = 711)	1,594.31 ± 1,141.55 (n = 183)	1,689.21 ± 3,402.04 (n = 222)	1,112.47 ± 1,131.86 (n = 202)	1,331.14 ± 3,113.90 (n = 105)	2.38	0.068
LF (n = 711)	432.36 ± 374.59 (n = 183)	481.43 ± 883.68 (n = 222)	309.53 ± 504.55 (n = 202)	375.91 ± 1267.19 (n = 105)	1.91	0.126
HF (n = 711)	383.97 ± 389.32 (n = 183)	337.13 ± 393.25 (n = 222)	260.83 ± 452.83 (n = 202)	311.79 ± 1105.48 (n = 105)	1.56	0.197
LF/HF (n = 711)	5.49 ± 49.33 (n = 183)	1.91 ± 2.05 (n = 222)	1.94 ± 2.47 (n = 202)	1.99 ± 2.11 (n = 105)	0.91	0.438

SD, standard deviation; SDNN, Standard deviation of normal-to-normal interval; RMSSD, The square root of the mean squared differences of successive NN intervals; TP, total power; LF, low frequency; HF, high frequency.

Table 5. The results of quantile regression analysis (50th)

Dependent variables	Quantile regression analysis (50th) in men					Dependent variables	Quantile regression analysis (50th) in women				
	Independent variables	β	SE	t	P value		Independent variables	β	SE	t	P value
SDNN (n = 1,338)	HR	-0.601	0.027	-21.89	< 0.001	RMSSD (n = 478)	HR	-0.593	0.045	-13.12	< 0.001
	Age	-0.520	0.042	-12.37	< 0.001		Age	-0.638	0.056	-11.35	< 0.001
	BMI	-0.200	0.081	-2.47	0.014		BMI	0.457	0.196	2.33	0.020
	SBP	-0.042	0.024	-1.75	0.080		SBP	0.030	0.028	1.05	0.295
RMSSD (n = 1,338)	HR	-0.632	0.028	-22.69	< 0.001	SDNN (n = 478)	HR	-0.736	0.045	-16.29	< 0.001
	Age	-0.444	0.040	-10.97	< 0.001		Age	-0.499	0.058	-8.57	< 0.001
	BMI	-0.186	0.094	-1.98	0.048		BMI	0.040	0.168	0.24	0.814
	SBP	-0.072	0.023	-3.22	0.001		SBP	-0.030	0.038	-0.78	0.436
TP (n = 1,334)	HR	-23.852	1.501	-15.89	< 0.001	TP (n = 478)	HR	-22.801	3.388	-6.73	< 0.001
	Age	-23.397	2.217	-10.55	< 0.001		Age	-29.344	3.638	-8.07	< 0.001
	BMI	-8.275	5.481	-1.51	0.131		BMI	17.134	12.432	1.38	0.169
	SBP	-3.615	1.627	-2.22	0.026		SBP	0.718	1.985	0.36	0.718

SE, standard error; SDNN, Standard deviation of normal-to-normal interval; RMSSD, The square root of the mean squared differences of successive NN intervals; TP, total power; HR, mean heart rate; BMI, body mass index; SBP, systolic blood pressure.

two most important determinants of the SDNN, RMSSD, and TP (Table 5).

DISCUSSION

In this study, we examined the normal ranges of various parameters of short-term HRV and the impact of gender and age on the values in a large Korean sample of healthy people. First, we suggest mean TP, LF, HF and LF/HF values of 1,358.9 ± 1,840.8 ms², 417.3 ± 807.6 ms², 254.1 ± 414.1 ms², and 2.4 ± 20.9 by frequency domain analysis and the mean SDNN and RMSSD values of 39.6 ± 22.1 ms and 29.7 ± 18.1 ms by time-domain analysis. Tsuji et al. (14) suggested the normative values for all eight HRV measurements. Their Ln-LF and Ln-HF values are higher than those derived in our study, and may be explained by the higher average age and ethnic difference in their study. Park et al. (11) suggested mean TP, SDNN, and RMSSD values of 1,106.9 ± 1,109.1 ms², 35.9 ± 15.5 ms, and 27.3 ± 15.6 ms, respectively, by time-domain analysis, and mean LF, HF, and LF/HF values of 287.5 ± 384.1 ms², 227.0 ± 284.4 ms², and 2.2 ± 3.4, respectively, by frequency-domain analysis in healthy Koreans. Although their findings are similar to our results, they are based on a relatively small sample size and thus cannot provide further information on the impact of demographic and clinical determinants.

Then, we analyzed whether the various demographic or clinical variables (gender, age, BMI, heart rate, blood pressure) influence HRV measurements. There were significant differences in HRV parameters between the genders, and after controlling for age, the statistical significance of those differences was changed slightly. Some studies have shown that HRV measurements are affected not only by age (14-17), but also by gender (17, 18). Especially, Ramaekers et al. (19) suggested that estrogens have a cardioprotective effect in women. Huikuri et al. (20) reported higher parasympathetic activity in postmenopausal women given hormonal replacement therapy; generally increased parasympathetic activity in women may be reflected by higher average HF and RMSSD values and the resulting lower LF/HF ratio.

As the 50th quantile regression analysis, the changes in the RMSSD depended on BMI in men but not in women, which is similar to previous study showing gender differences in BMI (18). Obviously, most HRV parameters depend on heart rate in both genders because HRV-estimating methods are based on heart rate. Muneta et al. (21) reported that approximately 80% of their patients with isolated systolic hypertension (ISH) showed a significant positive correlation between blood pressure and heart rate. These results suggest that blood pressure in patients with ISH is susceptible to fluctuations in ANS activity. In this study, the RMSSD and TP of the male participants depend on systolic blood pressure, which may be explained by the fact that the RMSSD and TP reflect the reactivity of cardiac rhythm.

Lastly, we analyzed whether various life habits influence HRV measurements. In this study, the SDNN, RMSSD and HF of the participants who habitually drank alcohol were significantly lower than those of the participants who did not. Further, the SDNN, RMSSD, TP, LF and HF values significantly increased with the exercise frequency. These findings are consistent with the reports of previous studies showing that exercise improve HRV by increasing the vagal tone (22) and habitual intake of alcohol negatively influences HRV by increasing autonomic instability (23).

Cagirci et al. (24) reported that the LF and LF/HF ratio are significantly higher and SDNN, RMSSD, and HF values are significantly lower in heavy smokers. Cigarette smoking induces functional changes in the cardiovascular system and these may reflect changes in a different organ system (e.g., the ANS influencing HRV) (25). We did not find the significant differences in the HRV parameters between the smokers and the non-smokers, which may be inconsistent with the results of previous studies. A possible reason for the lack of difference is that the history of

smoking was not strictly controlled.

Monda et al. (26) recently reported that espresso coffee influences parasympathetic activity in the supine position and Mattioli (27) reported the beneficial effects of coffee consumption due to anti-inflammatory actions mediated by antioxidants in the beverage. Rauh et al. (28) suggested that modest consumption of caffeine does not reveal negative or positive effects on HRV parameters in young and healthy habitual caffeine consumers. In our study, Ln-TP, Ln-LF, and Ln-HF values were significantly higher in the habitual coffee consumers. Further research is necessary to determine the effects of caffeine on HRV in habitual caffeine users.

This study has some limitations. First, the subjects were not randomly selected from the general population and there were more men than women. Approximately three-fourths of the subjects were permanent workers who underwent annual check-ups regularly, which are mandatory in Korea. As more men are employed in full-time positions, the gender disparity may reflect the reality. Second, the psychometric instruments were administered by only self-reports, and there is a possibility of missing past medical and psychiatric disorders. However, the possibility of selection bias is quite low because the subjects were healthy.

In conclusion, using a very large sample of healthy people, we have reported the normal ranges of HRV variables. Given that both clinicians and researchers are increasingly relying on short-term HRV assessment in measuring stress, our work suggest that age and gender should be considered as independent determinants for HRV.

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AUTHOR SUMMARY

Determinants for Heart Rate Variability in a Normal Korean Population

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In this study, we reported the normal ranges of short-term heart rate variability (HRV) variables in healthy Korean people, and analyzed whether the various demographic or clinical variables influence HRV measurements. There were significant differences in HRV parameters between genders and after controlling for age, the statistical significance of those differences was changed. Given that both clinicians and researchers are increasingly relying on short-term HRV assessment in measuring stress, our work suggests that age and gender should be considered as independent determinants for HRV.