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Reference ranges for autonomic function tests in healthy Korean adults

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Background: The standardized autonomic function test has become widely available. However, there are no reference data for this test for the Korean population. This study explored reference data for sudomotor and cardiovagal function tests for the Korean population.

Methods: The sweat volume by quantitative sudomotor axon reflex test, heart-rate response to deep breathing (HRdb), expiration:inspiration (E:I) ratio, and Valsalva ratio (VR) were measured in 297 healthy Korean volunteers aged from 20 to 69 years. Multivariate regression analysis was performed to evaluate the effects of age, sex, and body mass index on these variables. The 2.5th, 5th, 10th, 90th, 95th, and 97.5th percentile values were obtained for each investigation.

Results: The sweat volume was higher in males than in females. The HRdb and E:I ratio were negatively correlated with age, and were higher in males than in females. The VR was negatively correlated with age, but it was not correlated with sex.

Conclusions: This study has provided data on the reference ranges for sudomotor and cardiovagal function tests in healthy Korean adults.

Key words: Autonomic nervous system; Reference range; Sweating; Parasympathetic nervous system

INTRODUCTION

The autonomic nervous system is involved in several bodily functions, including regulating the blood pressure, pulse, body temperature, respiration, digestion, urination, and sexual function, and it is affected by various diseases. An autonomic function test is used to objectively assess these functions, and noninvasive and quantifiable tests have recently been developed and used due to advancements in technology.¹ Most of the previously published data on reference ranges are focused on Western populations,^{2,3} and there are almost no data available for Asians.⁴ However, autonomic function varies with race,⁵ and so reference ranges for autonomic function tests for Koreans are needed. A single domestic institute recently published reference ranges for sudomotor and cardiovagal functions according to age, sex, and body mass index (BMI).⁶ Rather than recruiting participants only from the single center, which would have been a limitation of the study, participants were additionally recruited from other centers. By so doing, the proposed reference ranges for autonomic function tests would be more representative of the Korean population.

MATERIALS AND METHODS

Participants

Tests were performed on 297 healthy volunteers (135 males and 162 females) in the neurology departments of six hospitals from March 2012 to May 2016. The included participants did not suffer from any neurological or systemic disorder and were not taking medication regularly. Participants with disorders that can affect the autonomic nervous system, such as diabetes, alcoholism, malnutrition, and anticancer therapy, were excluded. The participants were divided into groups based on sex and age. Clinical information such as age, sex, height, weight, and BMI were collected as the main outcome variables. Informed consent was obtained from all of the subjects.

Autonomic function tests

The tests were performed according to the "Guidelines for Autonomic Function Test" previously published in the Journal of Pain and Autonomic Disorders. The protocols of the

tests are described below.⁷

The quantitative sudomotor axon reflex test (QSART)

The QSART quantitatively assesses the postganglionic sympathetic cholinergic function and measures sweat volume after stimulating sweat glands using a 10% acetylcholine solution. In this study the QSART was applied to the medial forearm (at three-quarters of the distance from the ulnar epicondyle to the pisiform bone), proximal lateral leg (5 cm distal to the fibular head), distal medial leg (5 cm proximal to the medial malleolus), and proximal foot (above the extensor digitorum brevis muscle). The measurements were performed using the commercially available Q-Sweat[®] quantitative sweat measurement system (WR Medical Electronics Company, Maplewood, MN, USA), which was developed based on the principles of the QSART.

Heart-rate response to deep breathing (HRdb)

The HRdb test assesses the function of the parasympathetic nervous system based on the principle that the heart rate increases during inhalation and decreases during exhalation. The heart rate is measured during 5 seconds of inhalation and 5 seconds of exhalation, with these measurements repeated eight times. After a 2-minutes break, one more test is performed using a similar protocol. The five largest differences in heart rate during inhalation and exhalation from among the first eight measurements are selected and averaged. The expiration:inspiration (E:I) ratio is found by dividing the longest RR interval during expiration by the shortest RR interval during inhalation.

Valsalva ratio (VR)

The VR is determined by measuring the blood pressure and heart rate while blowing into a mouthpiece at a pressure of at least 40 mmHg for 15 seconds. This is repeated two more times after a 3-minute break. The VR is calculated by dividing the highest heart rate late during phase 2 with the lowest heart rate during phase 4.

Statistical analyses

Statistical analyses were performed using IBM SPSS (version 21.0, IBM Corp., Armonk, NY, USA) and MedCalc for Windows (version 17.5.3, MedCalc Software, Ostend, Belgium). Student's *t*-test or the Mann-Whitney *U* test was used to com-

pare continuous variables, while Fisher's exact test was used to compare categorical variables. Univariate and multivariate regression analyses with stepwise backward selection were then applied to the main outcome variables (age, sex, and BMI). In cases where sex significantly affected the results, males and females were analyzed as separate groups. In cases where age and BMI significantly affected the results, the median, 2.5th, 5th, 10th, 90th, 95th, and 97.5th percentile values were obtained, and a scatter plot and regression fit were produced. Upon performing the regression analysis, the following model assumptions were tested: linearity between the dependent and independent variables, normality of the error distribution, independence, and homoscedasticity of the errors. In cases where a model assumption was violated, data were transformed into logarithmic values to ensure that the assumption was satisfied. Internal validation was performed using the bootstrap method to confirm the appropriateness of the final model.

RESULTS

The participants were aged 41.6 ± 14.1 years (mean \pm standard deviation), and the males were younger than the females (39.6 ± 13.5 vs. 43.3 ± 14.4 years, $p = 0.036$). The BMI was significantly higher in males than in females (23.1 ± 3.0 vs. 22.3 ± 3.0 kg/m², $p < 0.001$; Table 1).

Table 1. Demographic characteristics of the participants

	Total (n = 297)	Males (n = 135)	Females (n = 162)	p-value
Age (years)	41.6 \pm 14.1	39.6 \pm 13.5	43.3 \pm 14.4	0.036
Age group (years)				0.093
20-29	80	45	35	
30-39	58	29	29	
40-49	57	24	33	
50-59	58	21	37	
60-69	44	16	28	
Height (cm)	165.5 \pm 8.6	172.6 \pm 5.8	159.6 \pm 5.7	<0.001
Weight (kg)	63.6 \pm 11.6	72.1 \pm 9.7	56.6 \pm 7.6	<0.001
Body mass index (kg/m ²)	23.1 \pm 3.0	24.2 \pm 2.6	22.3 \pm 3.0	<0.001

Values are presented as mean \pm standard deviation or number.

Sudomotor function

The sweat volume was higher in males than in females at all four measurement sites. The sweat volume for the forearm increased with age, but no association with age was observed for the other regions. The BMI showed a positive correlation with sweat volume in the proximal and distal legs. The regression equations for the four regions were as follows, where b0 is the intercept, b1 is Ln (age), b2 is sex (female), and b3 is Ln (BMI): forearm, b0 = -2.91, b1 = 0.62, and b2 = -0.57; proximal leg, b0 = -2.14, b2 = -0.72, and b3 = 0.76; distal leg, b0 = -2.72, b2 = -0.88, and b3 = 0.90; and foot, b0 = -0.95 and b2 = -0.64. The 2.5th, 5th, 10th, 90th, 95th, and 97.5th percentile values for the different measurement regions are presented in Table 2.

Table 2. Sweat volume in the four tested regions according to sex

Percentile	Forearm	Proximal leg	Distal leg	Foot
Male:female				
2.5th	0.05:0.07	0.25:0.12	0.15:0.10	0.08:0.05
5th	0.08:0.09	0.36:0.17	0.17:0.11	0.08:0.05
10th	0.10:0.11	0.48:0.26	0.29:0.16	0.13:0.017
90th	1.85:1.14	2.90:1.41	2.54:1.25	1.07:0.56
95th	2.46:1.32	3.08:1.63	3.18:1.68	1.25:0.80
97.5th	2.77:1.57	3.24:2.69	3.94:2.37	1.34:0.91

Cardiovagal function

The HRdb and E:I ratio decreased as age increased, and were lower in females than in males. The VR showed a negative correlation with age only. None of the three variables were correlated with BMI. The regression equations for the three variables were as follows, where b_0 is the intercept, b_1 is Ln (age), and b_2 is sex (female): HRdb, $b_0 = 62.63$, $b_1 = -11.93$, and $b_2 = -2.18$ (Fig. 1); E:I ratio, $b_0 = 0.86$, $b_1 = -0.16$, and $b_2 = -0.04$ (Fig. 2); and VR, $b_0 = 1.32$ and $b_1 = -0.20$ (Fig. 3). The 2.5th, 5th, 10th, 90th, 95th, and 97.5th percentile values for the different age groups and sexes in each test are presented in Tables 3-5.

DISCUSSION

The results of the present study, which involved 297 participants, were similar to those of a previous domestic single-center study that involved 181 participants.⁶ Differences according to sex were clearly observed in all of the variables except for the VR. Decreased autonomic function with increasing age was shown in the cardiovagal function test but not in the measurements of sweat volume.

The Mayo Clinic has suggested reference ranges for the QSART.² However, these reference ranges could not be used because most hospitals other than the Mayo Clinic use the

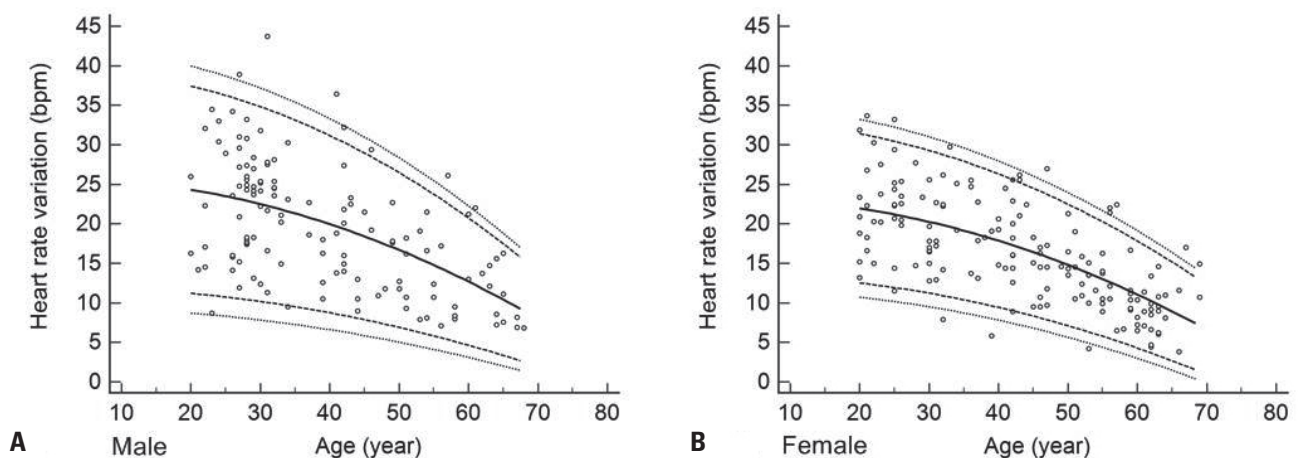


Fig. 1. Heart-rate response to deep breathing (HRdb) as a function of age for males (A) and females (B). The HRdb was negatively correlated with age and was lower in females than in males. Lines show 2.5th, 5th, 50th, 95th, and 97.5th percentiles. bpm, beats per minute.

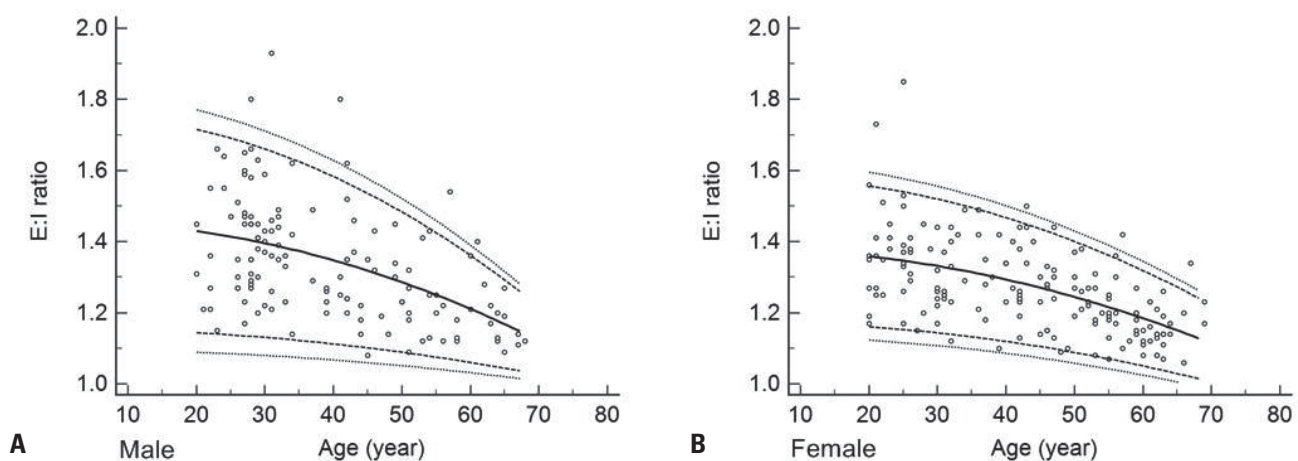


Fig. 2. Expiration:inspiration (E:I) ratio as a function of age for males (A) and females (B). The E:I ratio was negatively correlated with age and was lower in females than in males. Lines show 2.5th, 5th, 50th, 95th, and 97.5th percentiles.

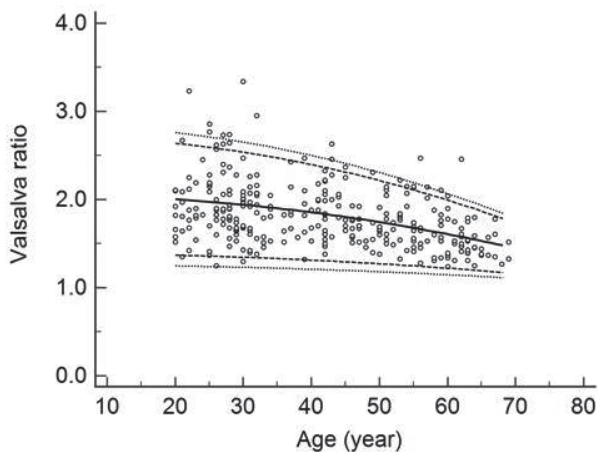


Fig. 3. Valsalva ratio (VR) as a function of age. The VR was negatively correlated with age. Lines show 2.5th, 5th, 50th, 95th, and 97.5th percentiles.

Q-Sweat system, which was developed using the QSART principle. The Mayo Clinic subsequently reported a relatively close correspondence between the Q-Sweat system and the QSART, but even that study did not suggest reference ranges for the Q-Sweat system.³ In a study of the quantitative autonomic function test, Novak suggested reference ranges for the Q-Sweat system for different age groups, but no specific statistical methods or percentiles were described.⁸ Therefore, the present study is significant because it suggests reference ranges for the sweat volume when using the Q-Sweat system that were obtained by applying statistical methods.

This study found that sex was a significant factor influencing the sweat volume, which is consistent with previous studies.^{2,4,9,10} However, the effect of age on sweat volume

Table 3. Heart-rate response to deep breathing according to age group and sex

Percentile	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years
Male:female					
2.5th	11.99:12.90	10.20:7.27	9.83:9.37	7.46:6.16	6.84:4.19
5th	13.25:13.98	10.82:9.86	10.54:9.50	7.82:6.64	6.87:4.49
10th	14.29:14.79	12.18:12.88	11.08:9.79	7.98:8.98	7.02:5.48
90th	32.73:30.03	28.54:25.52	29.00:25.49	19.58:20.38	19.24:13.88
95th	34.05:32.36	31.20:25.96	31.92:25.87	21.96:21.58	21.44:14.81
97.5th	34.48:33.29	35.37:27.25	34.09:26.38	24.03:22.06	21.72:15.64

Table 4. Expiration:inspiration ratio according to age group and sex

Percentile	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years
Male:female					
2.5th	1.17:1.17	1.18:1.11	1.11:1.10	1.10:1.08	1.10:1.07
5th	1.20:1.17	1.20:1.14	1.14:1.12	1.12:1.10	1.10:1.07
10th	1.22:1.19	1.22:1.18	1.15:1.13	1.12:1.13	1.11:1.08
90th	1.64:1.52	1.52:1.44	1.50:1.43	1.41:1.34	1.33:1.23
95th	1.66:1.61	1.61:1.47	1.61:1.44	1.44:1.37	1.37:1.25
97.5th	1.66:1.75	1.72:1.49	1.70:1.45	1.49:1.39	1.39:1.29

Table 5. Valsalva ratio according to age group

Percentile	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years
2.5th	1.37	1.34	1.42	1.32	1.25
5th	1.42	1.40	1.47	1.34	1.27
10th	1.54	1.45	1.52	1.40	1.31
90th	2.62	2.27	2.26	2.13	1.79
95th	2.73	2.47	2.34	2.15	1.89
97.5th	2.77	2.76	2.42	2.19	2.03

is unclear. Three studies conducted in the Mayo Clinic have produced variable results regarding the effect of aging.^{2,9,10} Furthermore, a study involving Chinese participants found a decreasing trend with age only in the foot region.⁴ This may be attributable to the effects of race on sudomotor function.^{11,12} In the present study, sweat volume increased with age in the forearm, whereas at other sites there was no influence of age. The effects of aging and race on the results obtained using the Q-Sweat system therefore need to be further evaluated.

HRdb was negatively correlated with age, which confirms the findings of previous studies.^{2,10,13,14} However, unlike in other studies, HRdb was lower in females than in males in the present study. The cutoff values of the 5th percentile in the USA and African studies were similar to those for the male group in our study.^{2,14} Aged females tended to show a lower HRdb, which may be caused by poor compliance. The effect of age on VR is controversial,^{2,10,13,15} and our study found a negative correlation between age and VR.

The BMI was not considered when interpreting the autonomic function tests because it did not show a clear association, except partly when using the Q-Sweat system. However, the participants of the present study showed a relatively uniform range of BMI values, with almost no obese participants. It has been reported that cardiovascular function deteriorates in people who are overweight or obese,¹⁶ and so caution is required when interpreting our results related to the BMI.

The lack of a disease control group in this study made it difficult to determine the optimal cutoff value. Based on previous studies and our experience, we recommend reference values of the 5th percentiles for the Q-Sweat system, HRdb, E:I ratio, and VR.

The present study was subject to some limitations. First, the included subjects came mainly from a single hospital (GNUH). However, a standardized protocol was applied in all of the included centers, and so our findings can represent the reference ranges for the Korean population. Second, the validity or diagnostic accuracy of reference values in patients with autonomic dysfunction was not assessed. Future studies should therefore include patient groups in order to confirm the findings of the present study.

The number of hospitals performing autonomic function tests is gradually increasing due to the increasing concern

about autonomic disorders. However, interpreting test results has thus far been difficult due to discrepancies in using reference ranges obtained from studies involving only Western populations. We believe that the findings of the present study will be helpful not only for patient treatment but also for research into autonomic disorders.

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Conflicts of Interest

The authors declare no competing financial interests.

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