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Effects of age, sex, and body mass index on sudomotor and cardiovagal functions in a healthy Korean population

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Abstract

Background: Hypertension results from an impaired baroreceptor reflex and enhanced sympathetic activity. The prevalence of hypertension differs among ethnicities and is more frequent in South Asians than in Caucasians, suggesting that baseline autonomic nervous system functions and their regulation may also differ among ethnic groups. In most studies, the reference values for clinical autonomic function tests are obtained from heterogeneous ethnic populations, or ethnic factors are not considered in the study design. Obtaining reference data in a homogenous ethnic group and comparing them within various ethnic groups could be helpful to detect ethnic differences in autonomic functions. The aim of this study was to identify normative reference values for standard autonomic reflex measurements in a homogeneous Korean population. *Methods:* A total of 181 healthy Korean volunteers (age, 20–74 years) underwent standard autonomic function tests: heart rate difference during deep breathing, Valsalva maneuver, and the quantitative sudomotor axon-reflex test. Mean and 5th and 95th percentile values were obtained for each age group. We also analyzed factors (age, sex, and body mass index) that can influence autonomic functions. *Results:* The heart rate difference during deep breathing and expiratory-inspiratory ratio were higher in males than in females and were inversely related to age. The Valsalva ratio was inversely related to age. Males had higher sweat volumes at all body areas evaluated than those of females, and only forearm sweat volume was significantly different between the age groups.
Conclusions: Cardiovagal function was affected by age and sex in Koreans. Sudomotor function was affected by sex, and only forearm sweat volume was affected by age and sex. These results represent preliminary normative clinical autonomic data in a Korean population comprised of a single ethnicity.

INTRODUCTION

The sympathetic nervous system and regulation of the baroreceptor reflex are key factors associated with blood pressure. Over-activated sympathetic tone induces high blood pressure and causes cardiovascular disease.[1] Many studies have reported that baroreflex sensitivity (BRS) is diminished in patients with hypertension.[2,3] Patients with renovascular hypertension, severe essential hypertension, and mild essential hypertension show that impaired BRS is related to the severity of hypertension rather than its etiology.[3]

The prevalence rates of hypertension and cardiovascular diseases differ among ethnicities. Asian populations have higher incidences of cardiovascular diseases, such as stroke, acute myocardial infarction, and heart failure.[4-6] In a study involving the St. Mary's stroke database, the South Asian subgroup showed significantly higher rates of hypertension, diabetes, and dyslipidemia compared with those of Caucasians.[7] Environmental factors, such as lifestyle and urban migration, as well as metabolic and genetic factors contribute to the development of cardiovascular disease.[8,9] As the prevalences of hypertension and cardiovascular disease differ among ethnic groups, baseline autonomic function or its regulation may also differ. However, few baseline/normative autonomic function data are available in different ethnic groups.

Autonomic function testing (AFT) represents noninvasive tests used to assess sympathetic and

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parasympathetic nervous system functions and are now being used to assess dysfunction in the autonomic nervous system (ANS) by examining sudomotor, cardiovagal, and cardiovascular adrenergic functions.[10] Abnormal findings are assessed by comparing observed and age-stratified references, as age greatly affects ANS function.[11]

AFTs are being performed much more widely in clinical practice with the commercialization of autonomic function testing equipment, but only a few studies have reported reference values for Asian populations. Although sweat gland function is believed to vary by ethnic group, studies on inter-ethnic differences are relatively limited.[12-14] To obtain normative AFT values among a homogeneous ethnic population, the present study assessed factors affecting ANS function by analyzing cardiovagal, cardiovascular adrenergic, and sudomotor functions in healthy Koreans without underlying conditions. Moreover, reference values for ANS functioning in a Korean population were produced to generate basic data for future inter-ethnic studies.

METHODS

Subjects

A total of 181 healthy volunteers (89 men and 92 women, aged 20–74 years) were recruited from March 2012 to May 2014 in the Neurology Department of Gyeongsang National University Hospital, with approval of the Institutional Review Board. All participants underwent a review of their medical history and a neurological examination by a neurologist. All participants were free of systemic and neurological diseases and were not taking any medications regularly. Subjects with diabetes, alcoholism, malnutrition, cancer treated with chemotherapy and/or radiotherapy, and other disorders that could affect the ANS were excluded from this study.

The participants were divided into five groups by age: Group A (20–29 years; 28 males and 15 females), group B (30–39 years; 17 males and 16 females), group C (40–49 years; 15 men and 20 women), group D (50–59 years; 17 males and 27 females), and group E (60–79 years; 12 males and 14 females).

Autonomic function tests

All participants fasted for 4 hours prior to testing and were prohibited from consuming alcohol or coffee 12 hours prior to testing. The AFTs were conducted in the following order: quantitative sudomotor axon reflex test (QSART), heart rate difference during deep breathing (HRdb), and the Valsalva maneuver (VM).[11]

1. Quantitative sudomotor axon reflex test

The QSART is a method used to evaluate postganglionic sympathetic sudomotor axon function quantitatively using QSWEAT® (WR Medical Electronics Co., Maplewood, MN, USA). This test measures the sweat response (latency and volume) in all four extremities by stimulating the sweat glands with a 10% acetylcholine solution for 5 min using a multi-compartment cell. The areas measured were the medial forearm (three-fourths the distance from the ulnar epicondyle to the pisiform bone), proximal lateral leg (5 cm distal to the fibular head), medial distal leg (5 cm proximal to the medial malleolus), and the proximal foot (over the extensor digitorum brevis muscle).

2. Heart rate difference during deep breathing

The HRdb was determined by eight repetitions of a 5-s deep inspiration and 5-s maximum expiration maneuver. This cycle was repeated after a 2-min break. The heart rate difference between each inspiration and expiration was obtained, and the mean of the five values with the largest difference was calculated. The expiratory-inspiratory ratio (E:I ratio) was defined as the longest RR interval during expiration/the shortest RR interval during inspiration among five cycles of deep breathing.

3. Valsalva maneuver

The VM was conducted by asking the subjects to expire forcefully for 15 sec through a tube attached to a barometer, while maintaining pressure > 40 mmHg. Changes in heart rate and blood pressure during this procedure were monitored by electrocardiogram and a noninvasive blood pressure device. The same procedure was repeated three times at 2-min intervals. The values were obtained only when subjects maintained a minimum pressure of 30 mmHg for ≥ 10 s. The Valsalva ratio (VR) was calculated as the longest RR interval during phase IV/the shortest RR interval during phase II. Blood pressure recovery time, which quantifies cardiovascular adrenergic function, was measured as the time it took for the lowest systolic blood pressure during phase III to return to baseline blood pressure during VM.

Table 1: The demographic characteristics of participants

	Total	Male	Female	*F*	*Sig.*
Number	**181**	**89**	**92**		
Age (year)	42.82±13.64	41.21±13.67	44.32±13.52	0.183	0.133
Body Height (cm)	165.76±8.26	172.19±5.68	159.75±5.19	1.557	0.000*
Body Weight (kg)	64.72±11.26	72.66±9.34	57.32±7.09	4.514	0.000*
Body mass index	23.44±2.87	24.45±2.46	22.49±2.91	1.422	0.000*
Skin temperature (°C)	32.32±0.6	32.31±0.67	32.33±0.53	1.662	0.839

Data presented as mean±Standard deviation.
Abrreviations: cm, centimeters; Kg, Kilograms; Sig, significance tested by the T-test.
*Significant correlation at the 0.05 level (2-tailed).

Statistical analysis

Demographic subject data were compared using the two-sample *t*-test. All variables are presented as means ± standard deviation and percentiles (5^{th} and 95^{th}). The Kolmogorov–Smirnov test was conducted to test for normality. Spearman's correlation analysis was used to test for correlations between the AFT parameters and each variable. Multivariate analysis of variance (MANOVA) was performed to evaluate the correlations between the AFT parameters and age, sex, and body mass index (BMI). Post-hoc analysis was performed using Tukey HSD method. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of all subjects was 43.07 ± 14.00 years (range, 20–74 years), and no age difference was observed between men and women. The mean male BMI was 24.45 ± 2.46 kg/m^2, and the female BMI was 22.49 ± 2.91 kg/m^2 ($p < 0.05$; Table 1). Five participants were classified as obese according to the World Health Organization (BMI > 30 kg/m^2).[15]

Sudomotor function

The QSART was performed on the left forearm, proximal leg, distal leg, and foot area, and latency and total volume were measured. The mean volumes for each area by sex and age group are shown in Table 2. Males had significantly higher QSART volumes at all four body areas evaluated compared with those of females. Forearm sweat volume increased with age. MANOVA showed no correlation between BMI and QSART volume.

Table 2: Sweat onset latency and sweat volume over the four tested regions by gender

	Total	Male	Female	*F*	*Sig*
Number	**181**	**89**	**92**		
Onset latency (seconds)					
Forearm	162.37±64.00	170.01±82.46	154.72±36.39	3.876	0.052
Proximal leg	139.02±58.87	136.13±72.90	141.79±41.68	0.289	0.592
Distal leg	146.60±52.98	145.60±59.30	147.58±46.28	0.486	0.487
Foot	172.39±69.89	176.77±84.62	167.79±50.14	0.490	0.485
Total sweat volume (ml)					
Forearm	0.55±0.65	0.75±0.81	0.35±0.33	6.453	0.013*
Proximal leg	1.02±0.79	1.38±0.84	0.68±0.55	16.328	0.000*
Distal leg	0.80±0.64	1.14±0.71	0.46±0.29	32.190	0.000*
Foot	0.33±0.29	0.44±0.33	0.23±0.19	18.403	0.000*

Wilks's Lambda=.563(*F*=4.021, *p*<0.01, *partial eta square*=.437)
Abbreviations: Sig, significance tested by MANOVA.
*Significant correlation at the 0.05 level (2-tailed).

Table 3: Mean and percentile values of HRdb and E:I ratio by sex and age groups

Parameter	20s			30s			40s			50s			60s+		
	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
Male															
HRdb	23.19	14.20	34.30	22.49	10.50	43.70	19.36	10.50	29.40	13.21	7.90	26.10	11.24	6.90	22.00
EI ratio	1.42	1.21	1.66	1.40	1.20	1.93	1.32	1.08	1.62	1.23	1.09	1.54	1.19	1.09	1.40
Female															
HRdb	20.96	8.40	29.40	18.82	7.90	25.60	16.73	9.50	25.90	13.09	6.50	21.30	9.87	4.40	17.00
EI ratio	1.36	1.16	1.85	1.31	1.13	1.49	1.28	1.12	1.47	1.23	1.10	1.38	1.17	1.08	1.34

Abbreviations: HRdb, heart rate difference during deep breathing; E:I ratio, expiratory-inspiratory ratio

Cardiovagal function

The means ± standard deviation, 5th and 95th percentile values of HRdb, E:I ratio, and VR are shown according to age group and sex in Tables 3 and 4. HRdb and E:I ratio values were correlated with sex and age, but not with BMI. VR values correlated with age. MANOVA showed that younger subjects had significantly higher HRdb, E:I ratio, and VR values. The male groups had higher HRdb and E:I ratio values compared with those of females.

Cardiovascular adrenergic function

Blood pressure recovery time was correlated with age (r = 0.167, p = 0.044), but not with sex or BMI. However, MANOVA showed that blood pressure recovery time was not associated with age.

DISCUSSION

Cardiovagal indices, such as the HRdb, VR, and E:I ratio, decreased with age and decreased more in females than in males. On the other hand, the cardiovascular adrenergic indices, such as blood pressure recovery time, were not associated with age, sex, or BMI. Sweat volume in the forearm and distal leg increased with age, and total sweat volume in all areas was lower in females than in males.

Factors that may affect ANS function include sex, age, obesity, and ethnicity.[11,16] Age is one of the most significant factors affecting the ANS, particularly cardiovagal and sudomotor functions.[11] Many studies have indicated that the HRdb decreases gradually in a linear or log-linear relationship with age.[10,17,18] Cardiovagal function, as assessed by the HRdb and VR, decreased with age in the present study, which is consistent with previous reports. The main mechanism for the age-related decrease in cardiovagal function has been postulated to be reduced carotid artery compliance.[19]

Age also affects sudomotor function[11,13,20-22], as increasing age is associated with diminished sympathetic outflow, altered presynaptic neurotransmitters, reduced vascular responsiveness, and impaired downstream (endothelial and vascular smooth muscle) second-messenger signaling.[21] Moreover, since longer unmyelinated fibers are affected by age, the lower extremities are more affected than are the upper extremities.[20] A study in healthy Chinese participants reported that total sweat volume in the foot area diminishes with age.[13] Contrary to other studies, the present study showed that sweat volume in the forearm increased significantly with age. The differences

Table 4: Mean and percentile values of Valsalva ratio by age groups

Age	Valsalva ratio		
	Mean ± SD	5th	95th
20	2. 13 ± 0.42	1.56	2.77
30	2.02 ± 0.39	1.42	2.95
40	1.93 ± 0.3	1.52	2.46
50	1.76 ± 0.25	1.42	2.15
60+	1.55 ± 0.26	1.31	1.90

Abbreviations: SD, standard deviation

were statistically significant, but the age-related sweat volume distribution varied, which limit the interpretation of these findings. Therefore, further studies involving sweat tests performed on more subjects are needed.

Sex and age have large effects on ANS function. A test conducted by the Mayo Clinic (which did not factor in ethnicity) showed that the VR, but not the HRdb, differs by sex.[11] In the present study, the HRdb and E:I ratio showed similar significant differences based on sex. Thus, sex affected cardiovagal function, as also seen in the Mayo Clinic study. Another study reported that sweat volume was twice as high in males than in females.[11] Unlike previous studies, sweat volume and sex were found to be correlated in the Chinese, whereas age was correlated only partially with foot area sweat volume.[13] The present study also showed that sex was the strongest factor associated with sweat volume, and it was approximately twice as high in men as in women, with some differences between age groups. Sex strongly affects sweat volume in both Eastern and Western studies, whereas age has less influence on sweat volume in Asians. A previous study reported that sweat onset latency is not associated with sex or age.(13) The results of the present study were similar to those of previous reports in all areas except age, which showed a weak correlation with proximal leg latency ($r = -0.188$, $p = 0.023$).

The effect of body weight on the ANS is related mainly to cardiovascular responses.(23) Weight gain increases sympathetic nervous system activity and decreases the parasympathetic response.[23-25] In the present study, changes in ANS function based on obesity were not clear, as no accurate results were obtained due to the small number of obese subjects participating.

It is not well known whether ethnic differences affect ANS function. A 1990 study compared the sympathetic nervous system of Caucasians and African-Americans but did not find any differences.[26] The results of a QSART in 20 Koreans and 35 Malaysians showed an overall reduction in sweat gland function in Malaysians[16], which is best interpreted as a decrease in thermal sweating, resulting from sweat gland sensitivity to acetylcholine in Malaysians. This can be viewed as a physiological characteristic adaptive to the higher temperatures of the Malaysian environment. A comparison test of cardiac autonomic function in 76 Turkish and 73 Japanese metabolic syndrome patients showed, heart rate turbulence (HRT) and heart rate variability (HRV) was reduced in Turkish patients. There was no statistically significant difference in all HRT and HRV parameters between Control-Turkish (n=25) and Control-Japanese (n=25). Waist circumference was significantly higher in Turkish group, hence authors concluded that cardiac autonomic function difference was due to central obesity rather than ethnicity itself.[27]

We determined that age and sex were correlated with cardiovagal functions, such as the HRdb, E:I ratio, and VR. We also verified that sex was correlated with postganglionic sudomotor function as measured by total sweat volume. Cardiovascular function was not associated with age, sex, or BMI. This study is significant, because it obtained reference values by conducting clinical AFTs in a homogeneous ethnic population. Future studies are needed to collect nationwide data from the Korean population via a multi-center study to enable an investigation of differences in ANS function between Koreans and other ethnic groups through a direct comparison of clinical AFT reference values.

DISCLOSURE

Conflict of interest: None

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