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Cardiovascular autonomic nervous response to postural change in 610 healthy Japanese subjects in relation to age

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ABSTRACT

To determine the effect of aging on the cardiovascular response to postural change, we examined the cardiovascular sympathetic and parasympathetic response to active standing in 610 healthy Japanese subject (6-83 years) measuring the initial heart rate (HR) response for 3min in the supine and standing position, we also measured the coefficient of variation of R-R interval (CV_{R-R}). As a result, the cardiovascular response to active standing demonstrated a different change with aging between sympathetic and parasympathetic. Sympathetic function was in a sthenia state in young subjects, and that this function declined with age increasing. Whereas, parasympathetic function was immature enough to inhibit the sympathetic tone in young subjects and matured at 20 years of age, and had an ability to inhibit sympathetic tone. CV_{R-R} show a linear change that decline with age increasing. These results indicated that the cardiovascular parasympathetic response to active standing shows a characteristic change with aging that differ from cardiovascular parasympathetic at rest represented by CV_{R-R}. The present study is the first report to demonstrate the cardiovascular response to standing in relation to aging in large population. These results suggested that the cardiovascular response to postural change is dependent on subject's age.

1. Introduction

Measurement of initial heart rate (HR) response to postural change is the most simple and reliable method to clinically assess the incidence and severity of parasympathetic and sympathetic disorders in HR control (Wieling et al., 1985). The initial HR response on standing is usually bimodal in healthy subjects and occurs within about 30 sec (Borst et al., 1982; Borst et al., 1984; Dambrink and Wieling, 1987). The mechanisms of the initial HR response on standing have been described previously (Borst et al., 1982; Borst et al., 1984).

Wieling et al. (1984) and Dambrink and Wieling (1987) have reported that the circulatory adjustment to the stress of postural change differs markedly between young and elderly subjects. Thus, in assessing the HR response on standing, it is essential to compare responses in patients with those of control subjects of comparable age. Wieling (1988) established a database of the lowest normal score (Wieling et al., 1982) in healthy European subjects in the age range of 10 - 80 years old, calculating every 5 years old from their previous reports (Wieling et al., 1982; Dambrink and Wieling, 1987). This database has been used for assessing the autonomic neuropathy, especially a decline of the cardiovascular vagal function.

In recent years, various orthostatic intolerances have been reported (Almquist et al., 1989; Benditt et al., 1991; Streeten and Anderson, 1992; Low et al., 1995; Rowe et al., 1995; Furlan et al., 1998). This intolerance was seen frequently not only in adults but also in children and adolescents.

In addition, Tanaka et al. (1994) investigated cardiovascular responses, such as blood pressure and baroreceptor reflex sensitivity, to active standing in Japanese and Swedish pre-pubertal children. From their conclusions, it seems that the autonomic functions in the cardiovascular system largely depended on genetic factors and environmental variables. As discussed above, we should pay careful attention to a patient's age and race. However, there have been no reports examining the initial HR response on standing from subjects younger than 10 years and older than 80 years without intermittence in healthy Japanese people.

The purpose of the present study was to examine the effects of aging on the cardiovascular autonomic nerve function to postural change by measuring the initial HR changes after active standing in healthy Japanese subjects.

2. Materials and Methods

Six-hundred-ten healthy Japanese subjects (139 women, 471 men), ranging in age from 6 to 83 years (32.8 ± 22.6 years SD), participated in the present study. The characteristics [height, body weight, BMI] of subject in this study are shown in Table 1. The nature, purpose, and risks of the study were explained to each subject, and informed consent was obtained from all subjects at the time of enrollment. All subjects underwent a medical examination at the local hospital, company, or school. Subjects who were obese (body mass index greater than 25kg/m^2), had a history of diabetes

mellitus, cardiopulmonary, with neurological or other major systemic diseases, or subjects on medication that could influence autonomic-circulatory function were excluded from this study. All subjects were sedentary and did not participate in any program of regular exercise (more than twice weekly for about 1h). Subjects with orthostatic hypotension, as observed by the Schellong test, and subjects that took more than 5 seconds to stand up, were also excluded from this study. This study was conducted from 1994 to 2004.

2.1. Measurement of initial HR response on standing

In the present study, ultra early HR response on standing (UEHRS) refers to the measurement of initial HR change after standing to assess the cardiovascular autonomic nerve function and baroreceptor reflex to orthostatic stress.

The examinations were performed in the morning or afternoon, at least 2 h after a meal. All subjects were prohibited from performing physical exercise 2 h prior to the examination. The examination room temperature and humidity was kept at a constant 22 ± 2 ^{o}C and 50 ± 10 %. After a detailed explanation of the procedures, subjects were asked to lie supine for 5-10 min. The coefficient of variation of R-R interval (CV_{R-R}) was measured to quantitatively assess the autonomic nerve function in a resting position before standing. Care was taken to measure CV_{R-R} in the supine period before standing, while all the subjects were asked to breathe normally, to exclude a

respiratory arrhythmia effect. The subject was then asked to stand up as quickly as possible. The instantaneous HR changes were measured continuously for 3 min. The examination was performed three times with two minutes of supine rest between each test, and the median HR response was determined. All subjects were asked to breathe normally and to keep quiet and still both in the supine and standing position. The instantaneous HR was calculated from the beat-to-beat R-R interval as measured by electrocardiogram (FCP-2155, FUKUDA DENSHI Co., Tokyo, Japan; BMS-7201, NIHON KOHDEN Co., Tokyo, Japan) and digitized at 500Hz/sec for analyzing with signal processing software (gmview2, Sygnalis Co., Tokyo, Japan).

The following 6 parameters of UEHRS were determined and analyzed (Figure 1).

1) HR at rest (H_0) was calculated as the mean of 10 sec when the subjects rested in a supine position before standing. 2) Immediate HR increase on standing (ΔH_{im}) was determined by subtracting H_0 from the HR at the primary peak (A in Figure 1).

3) Maximum HR (H_{max}) was determined as the HR at the secondary peak (B in Figure 1).

4) Minimum HR (H_{min}) was determined as the HR at the valley after having shown Hmax (C in Figure 1).

5) H_{max}/H_0 ratio.

6) H_{max}/H_{min} ratio.

In addition, the lowest normal value (Wieling et al., 1982) of ΔHR_{max} (= H_{max} - H_0) and HR_{max}/HR_{min} ratio (= H_{max}/H_{min} ratio) in healthy Japanese subjects in the age range 6 - 83 was

calculated every 5 years. We compared the lowest normal score in healthy Japanese subjects with that in European subjects (Wieling, 1988).

2.2. Statistical Analysis

All subjects were grouped according to age: under 10 years (Group 1, n = 114), 10-19 years (Group 2, n = 165), 20-29 years (Group 3, n = 41), 30-39 years (Group 4, n = 41), 40-49 years (Group 5, n = 55), 50-59 years (Group 6, n = 100), 60-69 years (Group 7, n = 52), above 70 years (Group 8, n = 42). The value of the 6 parameters of UEHRS and $CV_{R\text{-}R}$ were calculated and expressed as means ± SD.

The age distribution was significantly skewed in this study. A nonparametric procedure (Kruskal-Wallis rank test) was therefore used to compare means in the different age groups. If this test was significant, a post hoc test (Tukey-Kramer test) was used to compare each group. The Mann-Whitney's U test was used to examine the gender differences in each age group. The lowest normal score of ΔHR_{max} and HR_{max}/HR_{min} ratio was calculated from the log-transformation (Wieling et al., 1982). A P-value of less than 0.05 was considered to be statistically significant. All stastical analyses were performed using Stat View software (version 5.0, SAS institute Inc).

3. Results

All subjects were grouped into age ranges of 10 years, and the sample size of the group containing subjects older than 80 years was very small (n=7). No significant differences for the 6 parameters of UEHRS and CV_{R-R} were found between the 70-79 year old subjects (n=35) and the 80 years and older subjects by Mann-Whitney's U test. Thus, the subjects that were older than 70 years were combined as Group 8 (n=42).

3.1. The six parameters of UEHRS and CV_{R-R} in 610 healthy Japanese subjects

No influence of gender difference in the 6 parameters of UEHRS was found in the different age groups, while a significant sex difference in CV_{R-R} was found only in Group 8 (Male 1.8 ± 0.7 vs. Female 2.5 ± 1.0, $P<0.001$) by Mann-Whitney's U test (Table 2). Therefore, the mean value in each age group was calculated the data combined with male and female in this study.

All results and stastical data by Kruskal-Wallis rank test and Tukey-Kramer test are shown in Table 3. The CV_{R-R} showed a linear change with age: the highest value was found in younger subjects (Group 1 and 2) and the lowest value in older subjects (Group 6-8). The H_0 and H_{min} showed a similar response: the highest value was found in Group 1, while the value significantly declined with age, increasing from 6-9 to 20-29 years (Group 1 vs. 3, $P < 0.01$, Table 3). No significant difference was found between the groups from Group 3 to Group 8. The ΔH_{im} was high

from Group 1 to Group 4 and declined significantly with increasing age from 40-49 years. The H_{max} was highest value in Group 1 and declined significantly with increasing age from 6-9 to 20-29 years, increased slightly from Group 3 (97 ± 10 bpm/min) to Group 4 (99 ± 12 bpm/min), declined with increasing age from 30-39 years. The H_{max}/H_0 ratio and Hmax/Hmin ratio increased with increasing age from 6-9 to 20-29 years and decreased with increasing age. There was a significant peak in Group 3 (Group 3 vs. 1 and 8, $P < 0.01$).

3.2. The Lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} ratio in 610 healthy Japanese subjects

In this study, the lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} ratio in 610 healthy Japanese subjects in the age range 6 - 83 was calculated every 5 years [6-9 years (n = 114), 10-14 years (n = 82), 15-19 years (n = 83), 20-24 years (n = 25), 25-29 years (n = 16), 30-34 years (n = 16), 35-39 years (n = 25), 40-44 years (n = 27), 45-49 years (n = 28), 50-54 years (n = 60), 55-59 years (n = 40), 60-64 years (n = 25), 65-69 years (n = 27), 70-74 years (n = 20), 75-79 years (n = 15), 80-84 year (n = 7)] using the same method as described previously (Wieling et al., 1982).

The ΔHR_{max} and HR_{max}/HR_{min} ratio in healthy Japanese subjects showed a characteristic change with age. Both scores increased, starting from 6 - 9 year group, showed a peak in the 30 - 34 year group, and declined with increasing age from the 35 - 39 year group to the 80 - 84 year group. A linear change with age for both scores was found in a previous study (Wieling, 1988) but was not

found in this study (Figure 2 and Table 4).

4. Discussion

4.1 Initial HR response on standing in healthy subjects

Standing up in healthy subjects induced characteristic changes in HR. Immediately after standing, the HR started to increase abruptly towards a primary peak (ΔH_{im}), increased further to a secondary (maximum) peak (H_{max}), declined to a relative minimum (H_{min}), and then gradually rose again. The initial HR response was usually bimodal within about 30 sec in healthy subjects (Figure 1) (Borst et al., 1982, 1984; Wieling et al., 1983, 1984, 1985).

HR, in a supine position, (H_0) is mediated by the interaction between cardiovascular sympathetic nerve function and parasympathetic nerve function associated with the baroreceptor reflex (Robinson et al., 1966).

The immediate HR increase on standing (ΔH_{im}) is the result of abrupt inhibition of cardiovascular vagal tone and can be attributed to two operations; one is the central command (Freyschuss, 1970; Maciel et al., 1987; Martin et al., 1974) associated with the centrostaltic reflex, and the other is the exercise reflex (Freyschuss, 1970; Borst et al., 1972; Hollander and Bouman, 1975), which operates as soon as voluntary muscle contractions are performed (Borst et al., 1982).

ΔH_{im} represents the tonus of the cardiovascular parasympathetic nerve at rest and the efferent cardiovascular vagal inhibition (Borst et al., 1972; Hollander and Bouman, 1975). The primary HR increase (ΔH_{im}) is temporarily available to maintain cardiovascular output. Arterial blood pressure, however, will begin to fall markedly and is associated with a decrease in venous return (Loring, 1993).

The secondary HR increase (H_{max}) is mainly due to a further reflex inhibition of the cardiovascular vagal tone and can be attributed to the diminished activation of arterial baroreceptor by a temporary fall of arterial blood pressure (Loring, 1993; Shepherd et al., 1981). Thus, H_{max} represents baroreceptor sensitivity and cardiovascular sympathetic nerve tone.

The subsequent HR decrease after H_{max} (H_{min}) is associated with the recovery of arterial pressure and is again mediated through the arterial baroreceptor reflex by rapid vagal inhibition of the sinus node. H_{min} represents baroreceptor sensitivity and parasympathetic nerve tone.

The H_{max}/H_0 represents the afferent pathway function through arterial baroreceptors by a temporary fall of arterial blood pressure after standing.

The H_{max}/H_{min} ratio represents the functional relationship between an initial sympathetically mediated component caused by an initial fall in blood pressure and a vagally mediated component caused by a recovery of arterial pressure respectively.

It has been generally suggested that by measuring the 6 UEHRS parameters albeit is possible to assess the cardiovascular sympathetic/parasympathetic nerve function and baroreceptor reflex

response to postural change (Wieling et al., 1985).

4.2 Initial HR response on standing in 610 healthy Japanese subjects by UEHRS

We examined the cardiovascular autonomic nerve function to postural change in 610 healthy Japanese subjects aged 6 to 83 years using UEHRS. The principal results of this study are as follows:

1) The cardiovascular autonomic nerve function in a resting spine position (H_0); the cardiovascular sympathetic nerve function was in a sthenia state and the cardiovascular parasympathetic nerve function was in an immature state in young people, which would be insufficient to inhibit the cardiovascular sympathetic nerve tone. The cardiovascular parasympathetic nerve function matured around 20 years of age and can inhibit the cardiovascular sympathetic nerve tone.

2) The immediate primary HR increase on standing (ΔH_{im}); the cardiovascular vagal inhibition became mature with increasing age from 20 years of age. It maintained its function until 30 years and decreased after 30 with increasing age.

3) The secondary HR peak (H_{max}); the cardiovascular sympathetic nerve function was in a sthenia state in young people, and declined with increasing age. The Hmax decreased with increasing age from 6-9 years through to 20 years, and then increased slightly at 30 years. This was

associated with the cardiovascular parasympathetic nerve function through the maturation of the baroreceptor reflex at 20 years.

4) The subsequent HR decrease after H_{max} (H_{min}); it is conceivable that the cardiovascular parasympathetic nerve function and baroreceptor reflex after standing was in an immature state in young people, became mature at 20 years, and maintained a steady state from 20 years onwards.

5) The H_{max}/H_0 ratio and H_{max}/H_{min} ratio showed the highest value at 20-29 years. This result suggests that the cardiovascular sympathetic nerve function (H_{max}) declined with increasing age while parasympathetic nerve function (H_0 and H_{min}) became mature at 20 years. The cardiovascular autonomic function and baroreceptor reflex response to postural change, thus, showed a significant change up to 20 years.

4.3 The lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} in healthy Japanese subjects

Our result of the lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} in healthy Japanese subjects differed widely from the previous study (Wieling, 1988), especially in age group ranged from 10-14 years to 45-49 years. We are not aware of any publications showing a racial difference of cardiovascular response to standing from young people to elderly people. In order to explain the difference in this study, further investigations are needed to compare cardiovascular response to standing in Japanese and European subjects from the young to the elderly. However, a number of

possible explanations for this difference are as follows: 1) racial difference such as genetic and environmental factor; 2) difference in number of subject. As the former explanation, one study has reported that there was the genetic factor on the cardiovascular response to active standing. Tanaka et al. (1994) examined the cardiovascular response to standing between Japanese and Swedish pre-pubertal children. Their results suggested that Swedish children have an enhanced cardiovascular autonomic response, such as pronounced baroreflex receptor sensitivity and vasoconstrictor mechanisms. Although it seems difficult to specify genetic factor to explain difference between Japanese and European in previous study (Wieling, 1988), environmental factors are less likely to be relevant. Japan has recently experienced rapid changes in living and eating patterns, resulting in westernization. For example, fat intake doubled during the last 15years in Japanese adults (Shimamoto et al., 1989), resulting in a similar dietary pattern to western countries. Therefore, there is a small different in life style between Japanese and European. Furthermore, the experimental room condition was set the same temperature and humidity in previous study (Dambrink and Wieling, 1987). Thus, the difference in experimental condition may not be relevant both study. The latter explanation is a difference of the number of subject both experiment. The lowest normal score shows a widely different especially in age group ranged from 10-15years to 45-49 years. Wieling (1988) estimated the lowest normal score from their previous study (Wieling et al., 1982; Damblink and Wieling, 1987). The number of subjects in their previous studies was approximately 180 healthy European subjects aged from 10 to 89 years (Wieling et al., 1982: 10-29

years = 64, 30-49 years = 48, 50-65 years = 21; Damblink and Wieling, 1987: 10-15 years = 10, 60-69 years = 10, 70-79 years = 10, 80-89 years = 10). Whereas, we examined the 610 healthy Japanese subjects aged from 6 to 83 years. Moreover, the age distribution was different from previous studies (Wieling et al., 1982; Damblink and Wieling, 1987). There was a large number of subject aged from 6 to 49 years in this study [6-9 years (n = 114), 10-14 years (n = 82), 15-19 years (n = 83), 20-24 years (n = 25), 25-29 years (n = 16), 30-34 years (n = 16), 35-39 years (n = 25), 40-44 years (n = 27), 45-49 years (n = 28)], because it is from that point of view that a cardiovascular response to standing may have a transitional age in 20 years or thereabout. If a study is examined the cardiovascular response to postural change in same number of subject in Japanese and European, it seems probable that the lowest normal score may show a similar or higher score in European subject. For a fine example of this perspective, Tanaka et al. (1994) examined a cardiovascular response to active standing between Japanese (n = 53) and Swedish (n = 78) pre-pubertal children aged from 6 to 12 years. From their results, HR_{max}/HR_{min} ratio in Swedish children was significantly higher than Japanese. However, we cannot say for certain whether the different in this study is due to racial difference or not.

5. Limitation of test procedure

The limitation of this simple test procedure is the fact that blood pressure is not monitored on a

beat-to-beat base. When a normal initial HR response on standing is observed, it seems reasonable to infer that the underlying blood-pressure response is normal as well. An abnormal initial HR response on standing, however, can only be interpreted in a more general way. Sufficient information for classification of normal and abnormal orthostatic responses and selection of patients in need of further investigations, such as Finapres (Imholz et al., 1991), NIRS (Jobsis, 1977), power spectral analysis (Malliani et al., 1994) and PET (Ouchi et al., 2001) et al., can be obtained when the HR response on standing is combined with the conventionally measured steady state blood-pressure response. However, the simple test procedure is not sufficient for a full physiological interpretation in case of an abnormal test result.

In conclusion, we were able to demonstrate a change with aging of the cardiovascular response to standing in 610 Japanese healthy subjects aged from 6 years to 83 years using UEHRS. Based on our results we conclude that: 1) the cardiovascular sympathetic nerve function is mostly sthenia in young people, and the parasympathetic nerve function through baroreceptor reflex is immature enough to inhibit the sympathetic tonus. This effect declines with increasing age. 2) The cardiovascular parasympathetic nerve function through baroreceptors is the most mature at 20 years and sufficiently inhibits sympathetic tonus in the resting and standing position. 3) The efferent vagal pathway seems to be maintained from 6-9 years to 30-39 years and declines with increasing age from 40-49 years to 70-83 years. 4) The lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} in healthy Japanese subjects showed a characteristic change in age and differed from the findings in

European subjects (Wieling, 1988). It is difficult to interpret this difference but an important point to emphasize is that the cardiovascular autonomic function response to standing in Japanese shows a characteristic change in age, especially from 10 years to 20 years.

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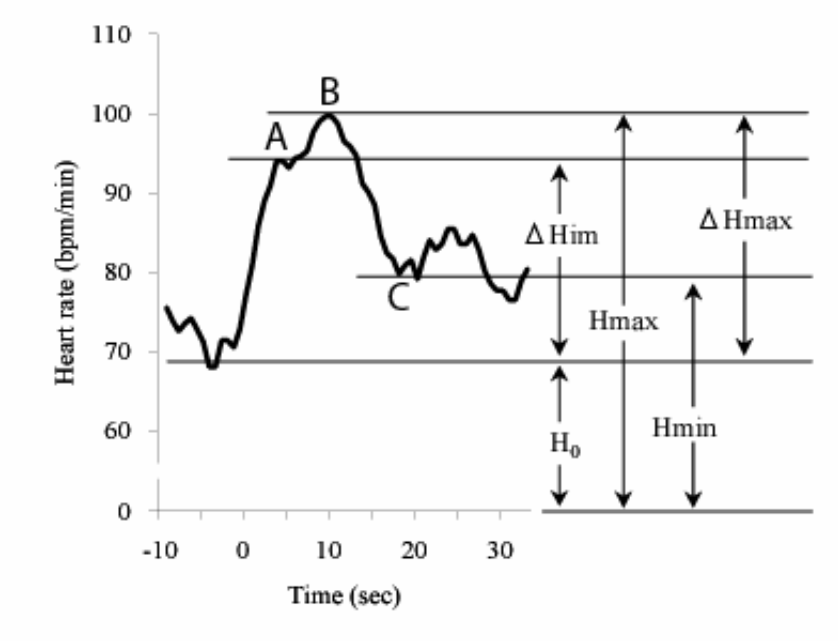
FIGURES AND FIGURE LEGENDS

Fig. 1. Example of HR changes evoked by standing up (solid line) in a 27-year-old female subject. The initial HR increase on standing is usually bimodal. The parameters of UEHRS and ΔHR_{max} (Wieling et al., 1982) are illustrated in this figure. H_0 is determined as the means for 10 seconds while the subject rests in a supine position before standing. HR_A and HR_B denote the primary peak (ΔH_{im}) and secondary peak (H_{max}), respectively. HR_C denotes a valley after H_{max} (H_{min}).

Fig. 2. The lowest normal score (below $P_{0.025}$) for ΔHR_{max} (A) and HR_{max}/HR_{min} ratio (B) were compared with results from a previous study (Wieling, 1988). The change with age for ΔHR_{max} and HR_{max}/HR_{min} ratio in the present study was different from those in the previous study. The score for all age ranges in the present study was higher than that from the previous study. ΔHR_{max} and HR_{max}/HR_{min} ratio was highest at 30-34 years in the present study. On the other hand, ΔHR_{max} and HR_{max}/HR_{min} ratio decreased with increasing age from 10-14 years to 75-79 years in the previous study.

Figure 1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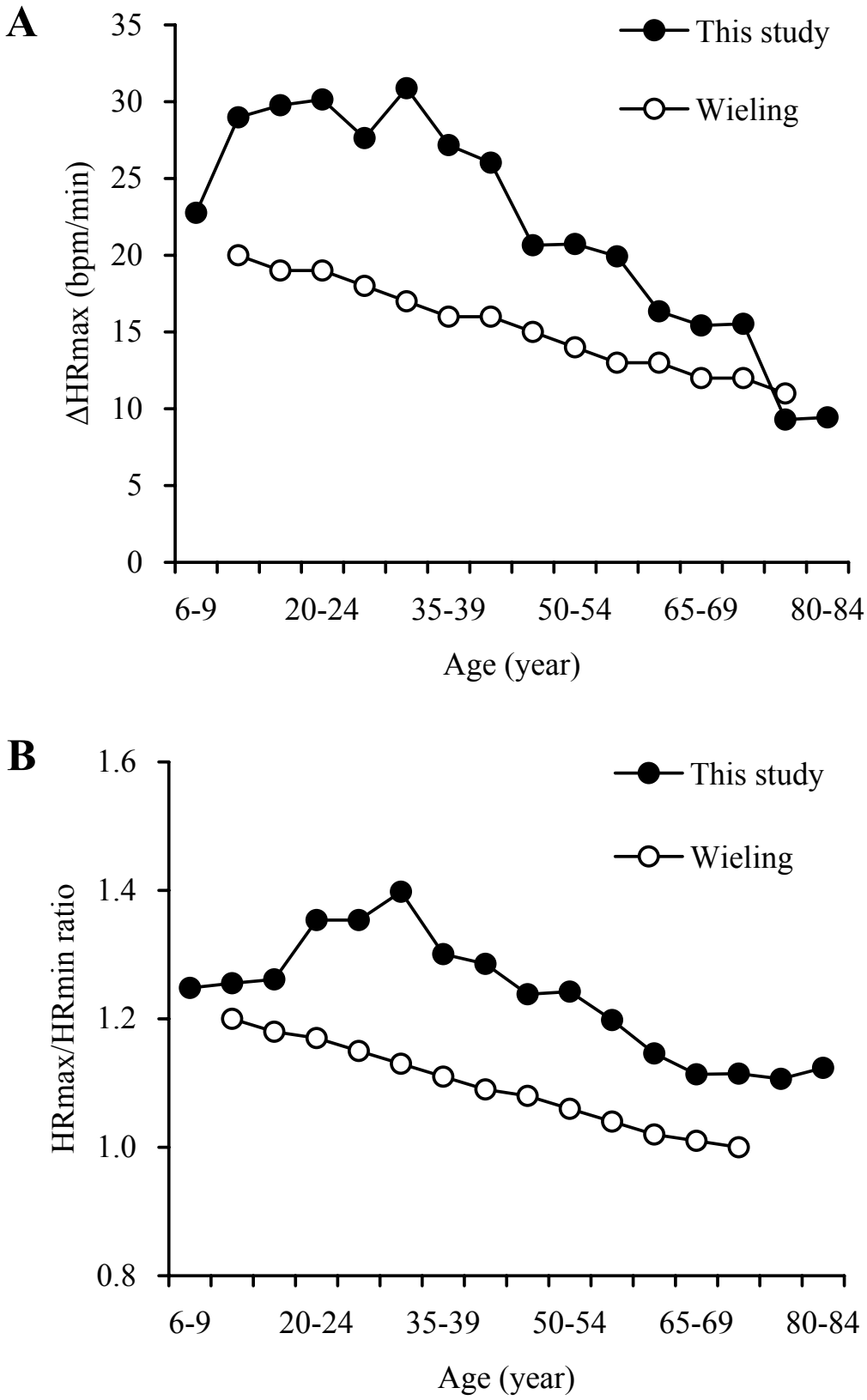
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ΔHRmax (bpm/min)
This study
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80-84
Age (year)
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1.2
1.0
0.8
HRmax/HRmin ratio
This study
Wieling
6-9
20-24
35-39
50-54
65-69
80-84
Age (year)

Table1. Subject characteristics

	Sex	N	Height (cm)	Body weight (kg)	BMI*
Group 1	M	114	124.5 ± 6.9	25.9 ± 4.0	16.6 ± 0.8
(6-9 years)	F	-	-	-	-
Group 2	M	148	160.1 ± 12.0	51.4 ± 10.2	19.8 ± 1.2
(10-19 years)	F	17	153.1 ± 6.3	46.3 ± 6.3	19.6 ± 1.2
Group 3	M	32	171.1 ± 5.7	63.9 ± 5.4	22.5 ± 2.4
(20-29 years)	F	9	158.5 ± 5.6	51.2 ± 6.0	20.4 ± 2.3
Group 4	M	28	169.1 ± 3.7	67.0 ± 2.8	23.4 ± 1.5
(30-39 years)	F	13	156.2 ± 4.2	54.2 ± 2.5	22.2 ± 2.5
Group 5	M	33	169.3 ± 6.1	68.5 ± 5.8	23.6 ± 1.2
(40-49 years)	F	22	156.3 ± 5.4	54.9 ± 6.0	23.1 ± 1.6
Group 6	M	60	166.2 ± 6.0	64.8 ± 5.4	23.8 ± 1.1
(50-59 years)	F	40	153.2 ± 5.5	54.9 ± 6.1	23.1 ± 1.7
Group 7	M	21	163.1 ± 6.4	62.9 ± 8.7	23.6 ± 1.2
(60-69 years)	F	31	150.8 ± 5.3	53.9 ± 5.3	23.5 ± 1.4
Group 8	M	25	160.1 ± 6.2	59.0 ± 7.0	23.0 ± 1.8
(70-79 years)	F	17	146.3 ± 6.2	50.1 ± 6.1	22.3 ± 2.4

Results are expressed as mean ± SD.

* BMI: Body Mass Index= weight (kg)/ height(m^2)

Table 2. Sex different of six parameters of UEHRS and CV_{R-R} in 610 healthy Japanese subjects

Group	Sex	Group 1	Group 2		Group 3		Group 4		Group 5		Group 6		Group 7		Group 8	
Age (years)	M	8±1	14 ± 3		24 ± 3		35 ± 3		45 ± 3		54 ± 3		64 ± 3		75 ± 4	
	F	-	16 ± 2		25 ± 3		35 ± 3		44 ± 3		54 ± 3		65 ± 3		75 ± 4	
CV_{R-R} (%)	M	6.2 ± 1.5	6.3 ± 2.0	n.s	5.6 ± 2.2	n.s	4.3 ± 1.5	n.s	3.4 ± 1.6	n.s	2.7 ± 1.1	n.s	2.2 ± 0.8	n.s	1.8 ± 0.7	*
	F	-	5.5 ± 1.9		4.2 ± 1.6		4.2 ± 1.6		3.0 ± 1.2		3.1 ± 1.5		2.0 ± 0.7		2.5 ± 1.0	
H_0 (bpm/min)	M	87 ± 10	74 ± 12	n.s	66 ± 9	n.s	69 ± 11	n.s	68 ± 12	n.s	67 ± 10	n.s	67 ± 9	n.s	67 ± 9	n.s
	F	-	69 ± 11		66 ± 7		69 ± 6		70 ± 11		70 ± 11		68 ± 8		69 ± 10	
ΔH_{im} (bpm/min)	M	20 ± 6	21 ± 6	n.s	20 ± 6	n.s	22 ± 6	n.s	17 ± 6	n.s	17 ± 6	n.s	14 ± 5	n.s	13 ± 4	n.s
	F	-	25 ± 6		18 ± 7		20 ± 6		18 ± 7		17 ± 6		13 ± 4		13 ± 6	
H_{max} (bpm/min)	M	113 ± 12	105 ± 12	n.s	97 ± 11	n.s	100 ± 14	n.s	92 ± 13	n.s	90 ± 12	n.s	83 ± 13	n.s	84 ± 10	n.s
	F	-	105 ± 10		100 ± 8		99 ± 6		96 ± 11		89 ± 12		87 ± 11		88 ± 10	
H_{min} (bpm/min)	M	89 ± 13	83 ± 13	n.s	70 ± 11	n.s	74 ± 15	n.s	73 ± 14	n.s	73 ± 12	n.s	72 ± 12	n.s	76 ± 9	n.s
	F	-	77 ± 12		75 ± 9		72 ± 4		75 ± 10		72 ± 13		77 ± 12		77 ± 12	
H_{max}/H_0 ratio	M	1.30 ± 0.09	1.44 ± 0.13	n.s	1.49 ± 0.15	n.s	1.46 ± 0.12	n.s	1.38 ± 0.15	n.s	1.35 ± 0.12	n.s	1.26 ± 0.10	n.s	1.26 ± 0.09	n.s
	F	-	1.55 ± 0.22		1.54 ± 0.20		1.45 ± 0.14		1.39 ± 0.12		1.33 ± 0.09		1.28 ± 0.11		1.28 ± 0.11	
H_{max}/H_{min} ratio	M	1.27 ± 0.12	1.28 ± 0.13	n.s	1.40 ± 0.17	n.s	1.37 ± 0.16	n.s	1.29 ± 0.13	n.s	1.25 ± 0.12	n.s	1.17 ± 0.09	n.s	1.11 ± 0.05	n.s
	F	-	1.40 ± 0.20		1.34 ± 0.16		1.38 ± 0.11		1.29 ± 0.11		1.25 ± 0.13		1.13 ± 0.09		1.15 ± 0.10	

Results are expressed as mean ± SD. n.s = not significant, * = $P<0.05$ by Mann-Whitney's U test

Table 3. Six parameters of UEHRS and CV_{R-R} in 610 healthy Japanese subjects

Group	Group 1 (n = 114)	Group 2 (n = 165)	Group 3 (n = 41)	Group 4 (n = 41)	Group 5 (n = 55)	Group 6 (n = 100)	Group 7 (n = 52)	Group 8 (n = 42)	Significance (P)
Age (years)	8±1	14±3	24±3	35±3	45±3	54±3	65±3	75±4	
CV_{R-R} (%)	6.2 ± 1.5	6.3 ± 2.0	5.4 ± 2.2	4.2 ± 1.5	3.2 ± 1.5	2.9 ± 1.3	2.1 ± 0.7	2.1 ± 0.9	1 vs. 4-8* 2 vs. 3-8* 3 vs. 4-8* 4 vs. 6-8* 5 vs. 7,8*
H_0 (bpm/min)	87 ± 10	74 ± 10	66 ± 9	69 ± 10	68 ± 11	67 ± 10	67 ± 9	68 ± 9	1 vs. 2-8* 2 vs. 3, 5-8*
ΔH_{im} (bpm/min)	20 ± 6	21 ± 6	20 ± 6	21 ± 6	17 ± 6	17 ± 6	13 ± 5	13 ± 5	1 vs. 6-8* 2 vs. 5-8* 3 vs. 7,8* 4 vs. 5-8*
H_{max} (bpm/min)	113 ± 12	105 ± 12	97 ± 10	99 ± 12	94 ± 12	90 ± 12	85 ± 12	86 ± 10	1 vs. 2-8* 2 vs. 3, 5-8* 3 vs. 6-8* 4 vs. 6-8* 5 vs. 7-8*
H_{min} (bpm/min)	89 ± 13	83 ± 13	71 ± 13	73 ± 13	74 ± 12	72 ± 12	75 ± 12	76 ± 10	1 vs. 2-8* 2 vs. 3-7*
H_{max}/H_0 ratio	1.30 ± 0.09	1.44 ± 0.14	1.49 ± 0.16	1.45 ± 0.13	1.39 ± 0.14	1.34 ± 0.11	1.27 ± 0.10	1.27 ± 0.10	1 vs. 2-5* 2 vs. 6-8* 3 vs. 5-8* 4 vs. 6-8* 5 vs. 7,8* 6 vs. 7,8*
H_{max}/H_{min} ratio	1.27 ± 0.12	1.29 ± 0.14	1.39 ± 0.17	1.37 ± 0.15	1.29 ± 0.12	1.25 ± 0.12	1.15 ± 0.09	1.13 ± 0.08	1 vs. 3,4,7,8* 2 vs. 3,4,7,8* 3 vs. 5-8* 4 vs. 5-8* 5 vs. 7,8* 6 vs. 7,8*

Results are expressed as mean ± SD. * = P<0.01 by post hoc test (Tukey-Kramer test)

Table 4. The lowest normal score for ΔHR_{max} and HR_{max}/HR_{min} ratio in the present study were calculated from log-transformation (Wieling et al., 1982) and compared with previous study's (Wieling, 1988).

Age (years)	ΔHR_{max} (bpm/min)		HR_{max}/HR_{min}	
	Wieling	This study	Wieling	This study
6-9		23		1.25
10-14	20	29	1.20	1.26
15-19	19	30	1.18	1.26
20-24	19	30	1.17	1.35
25-29	18	28	1.15	1.35
30-34	17	31	1.13	1.40
35-39	16	27	1.11	1.30
40-44	16	26	1.09	1.29
45-49	15	21	1.08	1.24
50-54	14	21	1.06	1.24
55-59	13	20	1.04	1.20
60-64	13	16	1.02	1.15
65-69	12	15	1.01	1.11
70-74	12	16	1.00	1.11
75-79	11	9		1.11
80-84		9		1.12