Effect of aging on gender differences in neural control of heart rate

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1Institute of Neuroscience and 4Department of Physiology, Tzu Chi College of Medicine and Humanities, Hualien 970; 2Department of Neurology, Tzu Chi Buddhist General Hospital, Hualien 970; 3Yu-Chi Health Station, Nan-Tou 555; 5Community Medicine Research Center, National Yang-Ming University, Taipei 112; and 6National Research Institute of Chinese Medicine, Taipei 112, Taiwan, Republic of China

Kuo, Terry B. J., Tsann Lin, Cheryl C. H. Yang, Chia-Lin Li, Chieh-Fu Chen, and Pesus Chou. Effect of aging on gender differences in neural control of heart rate. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H2233–H2239, 1999.—To clarify the influence of gender on sympathetic and parasympathetic control of heart rate in middle-aged subjects and on the subsequent aging process, heart rate variability (HRV) was studied in normal populations of women (n = 598) and men (n = 472) ranging in age from 40 to 79 yr. These groups were divided into eight age strata at 5-yr intervals and were clinically diagnosed as having no hypertension, hypoten-
sion, diabetic neuropathy, or cardiac arrhythmia. Frequency-domain analysis of short-term, stationary R-R intervals was performed, which reveals very-low-frequency power (VLF; 0.003–0.04 Hz), low-frequency power (LF; 0.04–0.15 Hz), high-frequency power (HF; 0.15–0.40 Hz), the ratio of LF to HF (LF/HF), and LF and HF power in normalized units (LF% and HF%, respectively). The distribution of variance, VLF, LF, HF, and LF/HF exhibited acute skewness, which was adjusted by natural logarithmic transformation. Women had higher HF in the age strata from 40 to 49 yr, whereas men had higher LF% and LF/HF between 40 and 59 yr. No disparity in HRV measurements was found between the sexes in age strata $\geq$60 yr. Although absolute measurements of HRV (variance, VLF, LF, and HF) decreased linearly with age, no significant change in relative measurements (LF%, HF%, and LF/HF%), especially in men, was detected until age 60 yr. We conclude that middle-aged women and men have a more dominant parasympathetic and sympathetic regulation of heart rate, respectively. The gender-related difference in parasympathetic regulation diminishes after age 50 yr, whereas a significant time delay for the disappearance of sympathetic dominance occurs in men.

autonomic nervous system; gender difference; frequency domain analysis

HEART RATE VARIABILITY (HRV) has been categorized into high-frequency (HF), low-frequency (LF), and very-low frequency power (VLF) ranges according to its frequency (26). HF is equivalent to the well-known respiratory sinus arrhythmia and is considered to represent vagal control of heart rate (10). LF is jointly contributed by both vagal and sympathetic nerves (3). The ratio LF/HF is considered by some investigators to mirror sympathovagal balance (1, 20) or to reflect the sympathetic modulations (18, 20, 22, 26). Because it is accessible and noninvasive, frequency-domain analysis of HRV has gained its popularity with broad applications as a functional indicator of the autonomic nervous system (ANS). For example, HF has been shown to decrease in diabetic neuropathy (19, 26), whereas LF/HF is sensitive to postural change (20) and mental stress (23). Our laboratory has recently demonstrated that LF and HF are decreased by pentobarbital anesthesia in the rat (32). In a human study, we found that LF is eliminated in brain death (16) and can be used as a prognostic tool for the prediction of patient outcome in the intensive care unit (33). In contrast to the well-documented changes of HRV in response to many pathological states, however, we were surprised to find that the effect of gender on HRV is still unclear. For example, women have been reported to have a lower (30), similar (6), and higher (13) HF than men. Even the effect of the aging process on the gender-related difference is uncertain.

Analyses of HRV have been recommended for both long-term (24 h) and short-term (5 min) studies (26). Although 24-h analysis of HRV (6, 30) is helpful in increasing the frequency resolution, especially for the lower frequency power, its application in a normal volunteer is difficult to accomplish. For example, changes in the physical or mental states of the study subjects (20, 23), changes in environments (23), and even noises in the ambulatory recordings (17) may severely influence the results of HRV analysis. Because the ANS, which regulates HRV, is very sensitive to changes in the internal or external environments of the body, a strict experimental control must be done to study HRV. For this purpose, 5-min recording is more practical than 24-h recording. Besides, HRV has been known to change along with aging (21, 24, 34), and the effects of aging on gender differences should also be considered. In this study, we proposed to systemically evaluate the effect of gender on resting HRV in eight age strata covering 40–79 yr on the basis of short-term (5-min) recording of an electrocardiogram (ECG) acquired in a well-controlled environment. From this study, we hoped to clarify the effect of the two basic physiological parameters, namely, sex and age, on the resting state of HRV, which is related to tonic ANS regulation of heart rate.
MATERIALS AND METHODS

Study sample and experimental setup. The procedures used in this study were approved by the Human Research Committee of the National Yang-Ming University, Taipei, Taiwan. A total of 1,070 normal volunteers (598 women and 472 men), ages 40–79 yr, were randomly enrolled for this study. The population was distributed into eight strata based on 5-yr age intervals (Table 1). We excluded subjects with the following conditions, which affect cardiovascular fluctuations (18, 26): hypotension (systolic pressure <110 mmHg or diastolic pressure <60 mmHg), hypertension (systolic pressure >140 mmHg or diastolic pressure >90 mmHg) (11a), diabetic neuropathy, an implanted cardiac pacemaker, frequent occurrence of atrial fibrillation, premature atrial or ventricular contractions, or other forms of arrhythmia. Furthermore, no patients were receiving medication or using drugs reported to influence cardiovascular fluctuations, such as hypnotics or autonomic blockers. Informed consent was obtained from each participant.

A precordial electrocardiogram (ECG) was taken in the daytime from each subject for 5 min with subjects lying quietly and breathing normally. The raw ECG signals were recorded using an eight-bit analog-to-digital converter with a sampling rate of 256 Hz. The digitized ECG signals were analyzed on-line and simultaneously stored on removable hard disks for off-line verification. Signal acquisition, storage, and processing were performed on IBM PC-compatible computers.

Processing of ECG signals. The computer program for HRV analysis was modified from our previous method (16, 33) according to the recommended procedures (26). In the QRS identification procedure, the computer first detected all peaks of the digitized ECG signals using a spike detection algorithm (14) similar to general QRS detection algorithms. Parameters such as amplitude and duration of all spikes were measured so that their means and standard deviations (SD) could be calculated as standard QRS templates. Each QRS complex was then identified, and each ventricular premature complex or noise was rejected according to its likelihood in standard QRS templates. Each QRS complex was then identified, and each ventricular premature complex or noise was rejected according to its likelihood in standard QRS templates. The R point of each valid QRS complex was defined as the time point of each heart beat, and the interval between two R points (R-R interval) was estimated as the interval between current and latter R points. In the R-R interval rejection procedure, a temporary mean and SD of all R-R intervals were first calculated for standard reference. Each R-R interval was then validated: if the standard score of an R-R value exceeded 3, it was considered erroneous or nonstationary and was rejected. The average percentile of R-R rejection according to this procedure was 1.2%. The validated R-R values were subsequently resampled and interpolated at the rate of 7.11 Hz to accomplish the continuity in time domain.

Table 1. Age and gender distribution of study subjects

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–44</td>
<td>40</td>
<td>68</td>
<td>108</td>
</tr>
<tr>
<td>45–49</td>
<td>54</td>
<td>75</td>
<td>129</td>
</tr>
<tr>
<td>50–54</td>
<td>60</td>
<td>82</td>
<td>142</td>
</tr>
<tr>
<td>55–59</td>
<td>75</td>
<td>81</td>
<td>156</td>
</tr>
<tr>
<td>60–64</td>
<td>70</td>
<td>82</td>
<td>152</td>
</tr>
<tr>
<td>65–69</td>
<td>69</td>
<td>110</td>
<td>179</td>
</tr>
<tr>
<td>70–74</td>
<td>47</td>
<td>45</td>
<td>92</td>
</tr>
<tr>
<td>75–79</td>
<td>57</td>
<td>55</td>
<td>112</td>
</tr>
<tr>
<td>Total</td>
<td>472</td>
<td>598</td>
<td>1070</td>
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</tbody>
</table>

Table 2. Definitions for measurements of heart rate variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Definition</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance</td>
<td>ms²</td>
<td>Variance of R-R intervals over temporal segment</td>
<td>0.003–0.04 Hz</td>
</tr>
<tr>
<td>VLF</td>
<td>ms²</td>
<td>Power in VLF range</td>
<td>0.04–0.15 Hz</td>
</tr>
<tr>
<td>LF</td>
<td>ms²</td>
<td>Power in LF range</td>
<td>0.15–0.4 Hz</td>
</tr>
<tr>
<td>HF</td>
<td>ms²</td>
<td>Power in HF range</td>
<td>0.15–0.4 Hz</td>
</tr>
<tr>
<td>LF/HF</td>
<td>ratio</td>
<td>LF (ms²)/HF (ms²)</td>
<td></td>
</tr>
<tr>
<td>LF%</td>
<td>nu</td>
<td>LF power in normalized units: LF/(total power – VLF) × 100</td>
<td></td>
</tr>
<tr>
<td>HF%</td>
<td>nu</td>
<td>HF power in normalized units: HF/(total power – VLF) × 100</td>
<td></td>
</tr>
</tbody>
</table>

nu, Normalized units; VLF, very-low frequency; LF, low frequency; HF, high frequency.

RESULTS

R-R interval and HRV measurements. Whereas the distribution of the original R-R interval, LF%, and HF% exhibited no significant skewness, the histograms of variance, VLF, LF, HF, and LF/HF, however, were skewed significantly to the right (Fig. 1A). The skewness in distribution of variance, VLF, LF, HF, and LF/HF could be partially corrected by square root transformation (Fig. 1B) and could be further eliminated by natural logarithmic transformation (Fig. 1C).
The relationships among R-R interval and all measurements of HRV are described in Table 3. The HRV measurements can be grouped into two categories: absolute measurements (variance, VLF, LF, and HF) and relative measurements (LF/HF, LF%, and HF%). Among the four absolute measurements, LF exhibited the least correlation to R-R interval \((r = 0.41)\). Of the relative measurements, LF\% exhibited the least correlation with R-R interval \((r = -0.05)\). In other words, LF, either absolute or relative, was the most independent HRV measurement of the basal R-R interval. All of the absolute measurements were well correlated with each other \((r^2 \geq 0.5)\). VLF exhibited the best correlation with variance \((r = 0.89)\), compatible with the fact that the short-term variance is mostly contributed by VLF. LF\% and HF\% were well correlated with LF/HF \((r^2 \geq 0.5)\). However, the correlations between the absolute and relative measurements of HRV were weak \((r^2 < 0.5)\).

Differential effects of sex and aging. The age distribution for all participants was 59.4 ± 0.3 yr, which was similar to that for individual male and female populations (60.1 ± 0.5 vs. 58.8 ± 0.4 yr). The female population had higher HF and HF\%, whereas the male population exhibited larger LF/HF and LF\% (Table 4). It should be mentioned that there was no significant difference in mean arterial pressure between the male and female populations.

![Figure 1](http://ajpheart.physiology.org/)

Fig. 1. Frequency distributions and estimated skewness \((S)\) of all measures of heart rate variability. Histograms were produced before (A) and after square root (Sqrt; B) or natural logarithmic (ln; C) transforms from all data \((n = 1,070)\) subjects. R-R, mean of R-R interval; Var, variance of R-R interval; VLF, very-low-frequency power; LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of LF to HF; LF\%, normalized LF; HF\%, normalized HF.

<table>
<thead>
<tr>
<th>Table 3. Correlation coefficients among measurements of heart rate and heart rate variability</th>
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<tbody>
<tr>
<td>R-R (\text{ln} (\text{Var})) (\text{ln} (\text{VLF})) (\text{ln} (\text{LF})) (\text{ln} (\text{HF})) (\text{ln} (\text{LF/HF})) (\text{LF}%) (\text{HF}%)</td>
</tr>
<tr>
<td>R-R</td>
</tr>
<tr>
<td>(\text{ln} (\text{Var}))</td>
</tr>
<tr>
<td>(\text{ln} (\text{VLF}))</td>
</tr>
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<td>(\text{ln} (\text{LF}))</td>
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<td>(\text{ln} (\text{HF}))</td>
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<tr>
<td>(\text{ln} (\text{LF/HF}))</td>
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<tr>
<td>LF%</td>
</tr>
<tr>
<td>HF%</td>
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</tbody>
</table>

R-R, mean of R-R intervals; Var, variance of R-R interval. All correlations achieved statistical significance at \(P < 0.001 (n = 1,070)\) except between R-R and LF\% \((P < 0.05)\), between \(\text{ln} (\text{VLF})\) and HF\% \((P < 0.05)\), between \(\text{ln} (\text{Var})\) and \(\text{ln} (\text{LF/HF})\) \((P < 0.05)\), and between \(\text{ln} (\text{LF})\) and HF\% \((P < 0.05)\).
Most HRV measurements, except HF%, were statistically (P < 0.01) and negatively (r < 0) correlated with age, although the correlations were generally weak (r^2 < 0.5) (Table 5). Among all variables, ln(LF) best correlated with age (r = -0.42), with a coefficient of determination of 0.176, which means that 17.6% of ln(LF) may be explained by age. When ln(LF) of the male and the female populations was analyzed separately, the r^2 of female population (0.202) was larger than that of the male population (0.152). Similar findings were noted in other absolute measurements of HRV (Table 5).

Subjects between 40 and 79 yr of age were divided into eight age strata (Table 1) to compare the effect of gender on HRV within the different age groups (Fig. 2). ANOVA detected significant effects of age on all the relative measurements (LF/HF, LF%, and HF%) (P < 0.001) and significant effects of gender on all the relative measurements (LF/HF, LF%, and HF%) (P < 0.001) and HF% (P < 0.05). For women, significant changes from the age stratum of 40 yr were not detected until the age strata of 50yr for variance, LF%, and HF%. For men, significant changes in variance, LF%, and HF% were not detected until the age strata of 60 yr. When the effect of gender was analyzed for each age stratum, it was noted that women exhibited a greater absolute HF at ages 40–49 yr. Dramatic disparities between genders were detected in LF/HF, LF%, and HF% at ages 40–59 yr, when men had higher LF/HF and LF% and lower HF%. All differences disappeared in the age strata ≥60 yr.

**DISCUSSION**

This study determined the various parameters of HRV in a large population of normal humans between 40 and 79 yr of age, from which the effects of gender and aging on cardiac sympathetic and parasympathetic controls were evaluated. The neural regulation of heart rate was analyzed by frequency-domain analysis of short-term HRV from supine rest in the daytime. Among all standard HRV measurements recently defined (26), we found that log-transformed LF best correlates with age. Women had a higher HF in the age strata of 40–49 yr, whereas men had higher LF% and LF/HF between 40 and 59 yr. There was no disparity in any HRV measurements between genders in subjects age ≥60 yr. Although absolute measurements of HRV (variance, VLF, LF, and HF) decreased linearly with age, no significant change in relative measurements (LF/HF, LF%, and HF%), especially in men, was detected until age 60 yr. We concluded that middle-aged women and men have a more dominant parasympathetic and sympathetic regulation of HR, respectively. The gender-related difference in the parasympathetic regulation diminishes after age 50 yr, whereas there is a significant time delay for the disappearance of sympathetic dominance in men. In terms of frequency-domain analysis, it is also worthwhile to note that among all short-term HRV measurements, the absolute measurements, especially LF, better reflect the aging process, whereas relative powers were superior at detecting the effect of gender.

It has been reported that HRV measured in subjects at supine rest in a quiet and relaxed atmosphere can be used as an assessment of vagal control of heart rate (10). More recently, transfer function analysis has shown that vagal control of heart rate can extend to both LF and HF. The sympathetic control, however, was limited to LF because of its frequency response (3). Therefore, the absolute measurements of HF in this...
study are considered to represent vagal control of heart rate, and LF is jointly contributed by sympathetic and parasympathetic nerves. Relative measurements (LF/HF, LF%, and HF%) appear to have provided quantitative evaluations of graded changes in the state of sympathovagal balance (1, 20). LF% and LF/HF have also been considered by previous investigators to reflect sympathetic modulation (18, 20, 22, 26). The physiological explanation of the VLF is much less defined (26). A recent study revealed that although VLF is influenced by the renin-angiotensin-aldosterone system, it depends primarily on the presence of parasympathetic outflow (27).

This study was undertaken to delineate the differential effects of gender and aging on frequency-domain parameters of short-term HRV based on a large population of normal humans. It is a complete comparison for all the short-term parameters, especially the relative powers, defined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (26). An intriguing and novel finding in the present study was that absolute measurements of HRV better reflected the aging process, whereas relative measurements were superior in detecting the effect of gender. It also is interesting to note the finding that middle-aged women and men have a more dominant parasympathetic and sympathetic regulation of heart rate, respectively, and that this gender-related difference eventually disappears in the advanced age groups.

There is gender-related difference in HRV are diverse in the literature. Bigger et al. (6) reported that men have larger LF and VLF than women, but they have similar HF. Huikuri et al. (13) reported that men have larger LF% and LF/HF but smaller HF. More recently, Umetani et al. (30) reported that HRV for all time-domain measurements is lower in women, especially below the age of 50 yr, and they believe the level of parasympathetic activity is lower in young women. Our result for middle-aged subjects is compatible with that of Huikuri et al. (13). We found that men exhibited larger LF/HF and LF% than women in the age strata of 40–59 yr, but women had higher HF in the age strata of 40–49 yr. The discrepancy between these studies may be partly due to the different experimental variables. Bigger et al. (6) and Umetani et al. (30) acquired ECG readings using a 24-h Holter monitor, whereas we and Huikuri et al. (13) collected ECG readings of subjects at supine rest in a quiet environment. Under the latter conditions, vagal activity becomes the major contributor to HRV (10), whereas sympathetic activity may contaminate LF of HRV, especially in an upright posture (20). Thus our results support the finding that the vagal modulation of HR is augmented in middle-aged women compared with men. In our study, the sympathetic dominance of men can be better demonstrated by
LF/HF and LF% in the age strata >50 yr, when the vagal indexes (e.g., HF and variance) between both genders are similar.

Respiratory sinus arrhythmia was reported to decrease age dependently in time-domain analysis, and this was subsequently confirmed by frequency-domain analysis (24, 34). We found that all indexes of vagal modulation of HR decline continuously with age, especially in women. In the literature, the role of the aging process in sympathetic modulation is more controversial. The catecholamine concentration has been reported to increase with age, whereas the receptor activity is downregulated (21). The LF/HF of HRV has been found to remain unchanged with age (34). In this study, however, LF/HF and LF% were found to decline significantly after age 60 yr, especially in men. Thus it is notable that sympathetic and parasympathetic modulations of HR appear to have different patterns in response to aging.

Although generated by complex interaction of sympathetic and parasympathetic functions, LF (log transformed) has the best correlation with age, indicating the advantage of LF over other HRV measurements in predicting the aging process of the ANS. In previous studies, LF was also found to be superior as a predictor of mortality (4, 6, 29, 33) and in the diagnosis of brain death (11, 16). Thus the combined analysis of sympathetic and vagal functions by LF is revealed to be more accurate in the prediction of mortality and aging. Unlike respiratory sinus arrhythmia, LF is not directly influenced by respiration, but it has been proposed that LF is generated from a complex feedback mechanism in the baroreflex loop (7). The finding that LF has the least correlation with basal R-R among all absolute measurements of HRV (Table 3) further indicates that LF is an independent index to basal cardiac rhythm.

Most current applications analyze absolute measurements of HRV without any mathematical (log, square root) transform. However, it has long been noted that HRV measurements seem to distribute in a nonnormal pattern, most likely logarithmic normal (5). In some studies, the HRV measurements have been square root transformed (12). The application of mathematical transform should be determined by the distribution pattern of each parameter. We therefore made a complete comparison for all short-term measurements of HRV under a variety of mathematical transforms (Fig. 1). We found that the distributions of original variance, VLF, LF, HF, and LF/HF were severely skewed, which could best be corrected by logarithmic transform. We also found that all absolute measurements of HRV and LF/HF correlated more significantly with age in their logarithmic transforms. These findings support the theory that absolute measurements of HRV should be log transformed to achieve normal distribution. Although normalized powers (LF% and HF%) also yield significant physiological information, the shapes of their distributions are less often discussed. Our data indicate that distributions of LF% and HF% are more like normal distributions and that the use of mathematical transform is not necessarily applicable.

The observation of respective dominances of parasympathetic modulation in women and sympathetic modulation in men before old age is interesting. It is compatible with the lower prevalence of cardiovascular disease in women before menopause in comparison with men. The complex age-gender interaction in the autonomic control of the heart and its relationship to cardiovascular diseases warrant further exploration.

We thank Dr. Cyprian V. Weaver for assistance in preparing the manuscript.

This study was supported by National Research Institute of Chinese Medicine Grant NRICM-86112 and National Science Council (Republic of China) Grant NSC-87-2314-B-320-006-M04.

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Received 9 February 1999; accepted in final form 23 July 1999.

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