Original Article

Age and Sex-Dependent Alterations in Heart Rate Variability: Profiling the Characteristics of Men and Women in Their 30s

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Abstract

Objective: The purpose of this study was to investigate age and sex-dependent changes in heart rate variability (HRV) in healthy subjects, specifically the changes during the third decade.

Methods: Heart rate (HR), standard deviation of N-N interval (SDNN), high-frequency (HF), low-frequency (LF), total-power (TP), and ratio of LF and HF (LF/HF) were computed in 99 healthy subjects (Male: 64, Female: 35) using the APG Heart-Rater (Tokyo-Iken, Co., Ltd., Inagi-city, Tokyo). HF, LF and LF/HF ratio were logarithmically transformed before analysis, and regression analysis was performed to evaluate the correlation between age and heart rate dynamics. Subjects were subsequently divided into 3 groups based on age (twenties, thirties, and forty-plus) and gender, and multiple comparisons between the age groups were carried out.

Results: All HRV parameters except Ln LF/HF ratio showed significant negative correlations with age in both men and women, and all of the correlations were stronger in men than women. Men demonstrated higher values than women across all HRV parameters during twenties and thirties, whereas each of the HRV parameter of women was higher than men in the forty-plus group.

Conclusion: In general, autonomic and parasympathetic activities attenuate with age in both genders. A significant decline in overall autonomic and parasympathetic functions of men in their thirties may be associated with the feeling of sudden decrease in physical strength after age 30. Conversely, a more gradual decline in total autonomic and parasympathetic functions in women in later life may account for their greater longevity than men.

KEY WORDS: age, sex, autonomic nervous system, heart rate variability, HRV

Introduction

“Physical strength drops dramatically when people turn 30” is a common expression among men and women who have had first-hand experience of a conspicuous metabolic shift portending the dawn of aging upon entering the third decade. Although the precise mechanisms underlying the phenomenon remain uncertain, autonomic down-regulation appears to play a role in triggering the reduction in physical capacity.

Bodily functions deteriorate with aging. Besides the obvious changes in the skin, eyes, ears and hair, autonomic functions undergo similar modifications through the aging process as well¹⁾. The two subsystems of the autonomic nervous system (ANS), namely, the sympathetic and parasympathetic branches, work in tandem to balance and regulate autonomous functions such as respiration, circulation, metabolism and digestion. These modulations are essential in maintaining the internal homeostasis that any disturbances of sympathovagal balance hinder the capacity to acclimate to changes in the environment²⁾.

For instance, heart rate and respiration ordinarily increase during exercise like running and decrease immediately after cessation of exercise. However, the recovery rate of heart rate and respiration becomes blunted with age as a result of sluggish vagal response failing to check cardiac and respiratory activities. Alternatively, orthostatic maneuvers such as going from supine to standing may trigger dizziness more frequently with age, reflecting the diminished sympathetic tone in the modulation of blood pressure. An increased incidence of postural hypotension with maturity is a well-established phenomenon³⁾ especially in women⁴⁾.

As mentioned above, many biological functions are under the control of coordinated autonomic activity. Sympathetic and parasympathetic capacities mature with time, but the degree of changes due to aging is different for the two subsystems owing to their divergent neural pathways. Consequently, sympathovagal balance also fluctuates with the change of time. Shimazu T *et al.* have reported an increase in basal sympathetic nervous activity due to senescence, but that the reactivity of the two branches declines over time¹⁾.

Interestingly, aging appears to induce gender specific alterations in the autonomic nervous system. In recent years, andropause has garnered nearly as much attention as its counterpart menopause. Age-associated impairment of autonomic capacity and target organs results in neuroendocrine imbalance. Given that sex hormones produce characteristic effects in men and women, autonomic decline and imbalance are expected to induce gender specific patterns of change as well. The mechanisms accounting for gonadal steroids on the autonomic nervous system have generally required animal or tissue studies. Such experimental data highlight the central and peripheral effects of estrogen^{5,6}. When male rats were given intravenous or intracerebral administration of estrogen, vagal tone acutely increased and sympathetic efferent activity was suppressed, and these effects were abolished following intracerebral administration of selective estrogen receptor antagonists⁶.

Several reports from human studies on sex-related differences in HRV frequency-domain parameters provide conflicting results. For example, Narkiewicz *et al.* reported that aging was accompanied by a greater increase in sympathetic activity in women than in men, independent of menopausal status⁷. However, many more studies have consistently depicted a parasympathetic tilt in women and sympathetic dominance in men^{4,8-10} during day- and nighttime¹¹ in their twenties and thirties^{8,11}. After age 50, the disparity in autonomic nervous activity appears to diminish^{12,13}. Accordingly, separate evaluations of autonomic regulation for men and women become necessary.

In this study, we have focused on elucidating age-related changes during the thirties compared with the decades before and after. More specifically, a comparative analysis of age-related autonomic modulations between men and women has been evaluated to highlight gender-specific drifts.

Subjects and Method

1. Heart Rate Variability Analysis

Analysis of heart rate variability (HRV) includes time and frequency domain measures. Standard deviations of N-N interval (SDNN) derived from time-domain analysis is thought to reflect heart rate fluctuations initiated by respiratory sinus arrhythmia. SDNN is considered by some investigators to mirror parasympathetic activity¹⁴.

Power spectral analysis of time indices yields frequency domain measurements¹⁵. Total power (TP), the overall spectral power, is regarded as an index of comprehensive autonomic activity¹⁶.

Additionally, HRV is categorized into three levels of power: high-frequency (HF), low-frequency (LF) and very-low frequency (VLF). As with SDNN, HF denotes components derived from respiratory sinus arrhythmia and is considered to represent vagal control. LF is jointly contributed by sympathetic and vagal nerves and represents the feedback regulation of blood pressure. Currently VLF is utilized solely for the standardization of LF and HF as its physiological significance is much less defined¹².

2. Study Population

Study participants included healthy volunteers aged 21 to 68 (64 men, 35 women) who provided oral consent. Blood pressure

measurements and blood tests of all the participants were performed at Kobayashi Medical Clinic (Shinjuku-ku, Tokyo). Those with clinical evidence of cardiovascular disease such as hypertension and hypercholesterolemia, diabetes or other significant disease requiring medication which interferes with the objectives of the study were excluded. **Table 1** summarizes the age and gender distribution of subjects.

Table 1 Age and gender distribution, and mean age of study subjects

	Male	Female	Total
20s	29	9	38
30s	15	13	28
40+	20	13	33
Total	64	35	99
Avg $\pm$ SD	34.3 $\pm$ 11.8	40.1 $\pm$ 13.4	36.4 $\pm$ 12.7

3. Method

Resting HRV was measured in a sitting position with the APG Heart Rater SA-3000P (Tokyo-Iken Co., Ltd., Inagi-city, Tokyo) to determine age-related fluctuations of HRV in healthy male and female volunteers. 3-min measurements were taken with a probe attached to the tip of the subject's left finger. Time domain analysis of HRV and power spectral analysis using the fast Fourier transformation were performed. Test measurements were taken in a temperature controlled room (24–26°C) at approximately 14:00 to accommodate for diurnal fluctuations.

4. Heart Rate Variability Parameters

HRV parameters and their definitions are described in **Table 2**.

Table 2 Definitions of HRV parameters

Parameters	Unit	Definition	Frequency Domain Analysis
HR	BPM	Heart Rate(1 min.)	
SDNN	ms	Standard deviation of RR interval	
TP	ms ²	Total power of power spectrum	
LF	ms ²	Power spectrum of LF range	0.04-0.15 Hz
HF	ms ²	Power spectrum of LF range	0.15-0.4 Hz
LF/HF	Ratio	LF(ms ²)/HF(ms ²)	

5. Data Analysis

First, the frequency-domain variables (TP, LF, HF and LF/HF ratio) were logarithmically transformed (Ln TP, Ln LF, Ln HF and Ln LF/HF ratio) to correct the skewness of distribution. Next, regression analysis was performed to determine the relationship between age and heart rate, SDNN, Ln TP, Ln LF, Ln HF and Ln LF/HF ratio. Male and female subjects were stratified by age into three groups (twenties, thirties and forty-plus) and the mean values of each age stratum were calculated. Disparities among the age groups were analyzed via the Games-Howell procedure, while the Student's *t*-test was employed to delineate generational gender differences of each parameter. Statistical significance was assumed for $p < 0.05$ for both analyses. SPSS Ver.11.5 was employed to analyze the data.

Results

1. Distribution of Age and HRV Parameters and Regression Analysis

Gender-specific scatter plots and linear approximation between age and HRV variables are shown in [Figure 1](#). The results of regression analysis are summarized in [Table 3](#).

A moderate, positive linear correlation was observed between heart rate and age in men ($r=0.367$, $p=0.003$), but not in women ($r=-0.086$, $p=0.624$).

With the exception of Ln LF/HF ratio, all HRV parameters showed significant negative correlations with age ($p<0.05$) in both genders. No significant association was found between Ln LF/HF ratio and age in either gender (men: $r=0.060$, $p=0.636$, women: $r=0.077$, $p=0.659$).

Men demonstrated a very strong negative correlation ($-0.7<r<-0.5$) between age and SDNN, Ln TP, Ln LF and Ln HF. A particularly high correlation with Ln TP ($r=-0.665$, $p<0.001$) was noted and confirmed by the coefficient of determination value ($R^2=0.442$). These results indicated that 44.2% of Ln TP data were closest to the line of best fit.

Women also exhibited a moderate negative correlation ($-0.5<r<-0.3$) between age and all HRV indices, except for Ln LF/HF ratio. Although Ln TP ($r=-0.447$, $p=0.007$) demonstrated the strongest association, the coefficient of determination (R^2) of 0.200 suggested a lower degree of predictive accuracy from regression analysis than men.

The slope of the regression line for each HRV parameter was less steep in men than in women, except for Ln LF/HF ratio. Men demonstrated a greater proportion of decline in each parameter with advancing age.

2. Age Group Comparisons

Age-related changes in heart rate, SDNN, Ln TP, Ln HF, Ln LF, and Ln LF/HF ratio are shown in [Figure 2](#).

(1) Men

All HRV parameters, except for heart rate and Ln LF/HF ratio, displayed marked reduction with maturity. Furthermore, multiple comparison analysis revealed statistical disparities in heart rate between the twenties and forties-plus ($p<0.001$). Prominent differences in SDNN were noted between the twenties and thirties ($p=0.002$), and twenties and forties-plus ($p<0.001$). Significant differences in Ln TP were noted between the twenties and thirties ($p=0.034$), thirties and forty-plus ($p=0.020$), and twenties and forty-plus ($p<0.001$). Statistical differences in Ln HF were found between the twenties and thirties ($p=0.002$), thirties and forty-plus ($p=0.049$), and twenties and forty-plus ($p<0.001$) age groups.

Although the difference in Ln LF/HF ratio between the twenties and thirties was statistically irrelevant, 61.6% of the mean values demonstrated an increase. Forty-plus men showed a 36.3% reduction in Ln LF/HF ratio compared with men in their thirties, resulting in near equivalent level as men in their twenties.

Fig. 1. Scatter plots and linear approximation

Table 3 Regression analysis

		HR	SDNN	Ln TP	Ln LF	Ln HF	Ln LF/HF
Male	r	0.367	-0.618	-0.665	-0.563	-0.639	0.06
	R^2	0.135	0.381	0.442	0.317	0.409	0.004
	Intercept	55.228	122.183	10.005	8.77	8.397	0.375
	Slope	0.324	-1.715	-0.066	-0.072	-0.071	0.005
	p	0.003	0.000	0.000	0.000	0.000	0.636
Female	r	-0.086	-0.393	-0.447	-0.354	-0.408	0.077
	R^2	0.007	0.154	0.200	0.125	0.166	0.006
	Intercept	74.753	68.708	8.515	7.309	7.144	0.165
	Slope	-0.067	-0.61	-0.031	-0.032	-0.038	0.006
	p	0.624	0.020	0.007	0.037	0.015	0.659

(2) Women

All HRV indices besides Ln LF/HF ratio declined with advancing age. Multiple comparison procedures revealed a significant difference in Ln HF between the twenties and forty-plus ($p=0.045$), yet heart rate, SDNN, Ln TP, Ln LF, Ln HF and Ln LF/HF ratio did not differ considerably among the age groups. Ln LF/HF ratio of the thirties demonstrated a 79.1% reduction from the previous decade notwithstanding the statistical insignificance. After forty, Ln LF/HF ratio was 8.58-fold higher than the thirties and 79.8% greater than the twenties.

3. Gender Differences Among the Age Groups

The mean values of heart rate, SDNN, Ln TP, Ln HF, Ln LF, and Ln LF/HF ratio for all age strata are shown in [Table 4](#). In the youngest age group, men had higher mean values than women, except for heart rate and Ln HF. Significant male-female differences were noted in heart rate ($p=0.001$), SDNN ($p=0.014$) and Ln TP ($p=0.031$).

Men in their thirties demonstrated higher values than age-matched women across all HRV parameters, except for heart rate. Ln LF/HF ratio was 8.56-fold greater in men as well. However, gender differences were not statistically significant.

By the forties women outnumbered men in all measured variables, except for heart rate, even though gender differences were not statistically robust.

Discussion

1. Age-Related Changes in Heart Rate

Rosenblueth and Simeone propounded the following model to illustrate the relationship between autonomic modulation and heart rate¹⁷⁾:

$$HR = m \times n \times IHR$$

Heart rate was expressed as the intrinsic heart rate (IHR) (unique beat-to-beat fluctuations independent of autonomic influence) multiplied by the two components of the ANS, the sympathetic ($m: m>1$) and parasympathetic ($n: n<1$), respectively. As is evident from the formula, heart rate is wholly influenced by autonomic activity.

A positive correlation was confirmed between heart rate and age in men ($r=0.367$, $p<0.01$: [Table 3](#)). The application of the Rosenblueth-Simeone model for these data showed that aging was accompanied by an increase in $m \times n$. Furthermore, an increase in $m \times n$ against a backdrop of parasympathetic activity (n) moderating the heart rate was surmised as the result of, at least in part, by an increase in sympathetic activity (m) with advancing age.

In contrast, no correlation was detected between age and heart rate in women ($r=-0.086$, $p=0.624$: [Table 3](#)) and only a minimal increase in heart rate with age was observed in age group comparisons. Analysis of these data using the Rosenblueth and Simeone model revealed negligible age-related variations in $m \times n$. However, because heart rate was influenced by the product of sympathetic and parasympathetic modulations, separate account of their activities was impossible to determine. In order to specifically measure the respective autonomic activities that could not be inferred from heart rate, HRV was used to quantify and interpret the results.

2. Age-Related Changes in Autonomic Functions

* Overall Autonomic Activity

The results of this study revealed that aging was accompanied by an overall decline in ANS activity in both men and women. Ln TP, the principal index of general sympathovagal tone, exhibited a moderately significant negative correlation with age in both genders (men: $r=-0.665$, $p<0.001$, women: $r=-0.447$, $p=0.007$: [Table 3](#)). Even though age-associated decline in Ln TP undergird previous findings^{12,18)}, Ln TP showing the strongest association with age among all HRV parameters was a novel finding from our study.

Based on the striking resemblance between Ln LF, an index of sympathovagal modulation, and Ln TP ([Figure 1](#), [Table 3](#)), Ln LF was seen as a potential indicator of ANS activity as a whole. The opinions on LF as a marker of sympathetic activity, however, are diverse in the literature^{13,18)}. If LF is translated as a benchmark of sympathetic activity, sympathetic capacity is also observed to decline with age but such implications require exploration in future studies.

* Sympathetic activity

In light of Ln LF/HF ratio, an index of sympathetic outflow, failing to demonstrate any correlation with age in both genders, and coefficient of determination yielding a low value ([Table 3](#)), age-related changes were assumed to progress in a non-linear fashion. On closer examination, multiple comparisons across the age strata revealed gender-specific variations.

In men, a sharp increase in sympathetic activity was observed during the thirties, while the forty-plus and twenties yielded similar values patterning an inverted U curve ([Figure 2](#)). By contrast, women demonstrated a J curve pattern with a transient decrease in the thirties followed by an abrupt increase after forty ([Figure 2](#)). In the past, Kuo *et al.* reported that Ln LF/HF ratio of both genders dipped during the fifth decade in their study of healthy subjects ages 40 and over¹²⁾. In addition, Zhang *et al.* documented an inverted U correlation between LF/HF ratio and age with the fifties as the apex¹⁸⁾ despite a lack of characterization of gender-specific changes. As such, age- and sex-associated changes in sympathetic activity observed in this study became potentially compelling evidence for further investigation.

Although the mechanism of sympathetic preponderance in men during the third decade remains elusive, a sudden sympathetic withdrawal after age 40 is attributed to the superimposition of environmental causes upon normal biological changes in later life. Men in their thirties suffer greater social burdens from work and family, and their lives are often punctuated by a myriad of environmental changes. Moreover, the wear and tear of daily life combined and little interest in health prefigure for an ineffectual health and stress management. According to the 2005 Mental Health Inventory of Labor Unions by the Japan Productivity Center for Socio-Economic Development (JPC-SED), “emotional disorders” are most often experienced by workers in their thirties (49.9%), surpassing the generations above and below¹⁹⁾. The psychosocial skills necessary to cope with increasing social demands are often lacking in this generation, which precondition the susceptibility observed during the thirties. By the fourth decade, having acquired sufficient social experience and skills to manage their stress, the augmented sympathetic tone during the thirties may revert back to its original level in men. However, in studies that investigate age-related changes using HRV, individual environmental influences are virtually impossible to eliminate.

Menopause appears to instigate a shift towards sympathetic dominance in women ages 40 and over. Although a separate analysis of menopausal women 45-55 yr was not conducted in this

Fig. 2. Age groups (*: $p<0.05$, **: $p<0.01$)

study as women over 40 were combined into a single group, Kuo *et al.* reported that Ln LF/HF ratio was observed to peak during 45-49 yr and conspicuously drop during 55-59 yr¹²⁾. This shift has been ascribed to a reactivation of sympathetic dominance during the menopausal years.

* Parasympathetic activity

SDNN and Ln HF, the two indices of vagal modulation, demonstrated negative correlations with age in both genders (Table 3). Consequently, parasympathetic activity was deduced to decline with age. These finding corroborate the results hitherto obtained in this study^{12,18)}.

In general, men demonstrated a stronger correlation than women of similar age range (Table 3). In light of the significant variances among the three groups (Figure 2), age-related loss of parasympathetic tone was far more prominent in men.

* Changes during the third decade

According to the results of the study, men experienced significant decline in overall autonomic and parasympathetic modulations during the third decade. Because depressed vagal tone indicates reduced inhibition of heart and respiratory rates, we postulated that the loss of post-exercise respiration and heart rate recovery with age precipitated the “abrupt decline in physical strength during the thirties”. Reports from research on chronic fatigue syndrome have confirmed a loss of parasympathetic function in patients with this syndrome²⁰⁾, and thereby underscore the correlation between reduced vagal capacity and the subjective experience of fatigue.

Improved autonomic functions are heralded as restoring the “sudden decrease in physical strength during the thirties”. Regular physical activity has been strongly recommended to minimize the loss of autonomic regulation. Carter *et al.* have reported that endurance training leads to an improvement in parasympathetic tone and inhibition of sympathetic excitation at rest²¹⁾. Additionally, Hottenrott *et al.* have reported that regular aerobic exercise improves HRV and checks the resting heart rate²²⁾. These findings strongly suggest the efficacy of regular physical exercise in restoring the ANS capacity.

No other studies to date have investigated the phenomenon of “sudden loss in physical strength during the third decade”. The efficacy of exercise in up-regulating the autonomic functions in this age group has also not been critically examined. Further investigation of the mental and physical effects of aging during the thirties must be clarified in order to advocate regular exercise as an effective tool for health management for the generation that will bear the burden of our society’s future.

* Gender differences in HRV

Based on the results of age-group comparisons, all HRV parameters were higher in men than in women during the twenties and thirties, which reversed during the forties (Figure 1). During the second decade, SDNN and Ln TP were remarkably elevated in men (Table 4), as were all other parameters despite the statistical insignificance. A similar gender skew in autonomic functions was noted during the thirties; however, by the fourth decade, women exhibited greater activity across all HRV parameters (Figure 2, Table 4). This reversal phenomenon was an intriguing finding from our study even though it is at odds with the relative parasympathetic preponderance in premenopausal women observed in other studies, as previously depicted.

Women are known to outlive men, possibly buffered by the autonomic advantages associated with long-term exposure to estrogen²³⁾. Moreover, some studies indicate that estrogen may act on nerve growth factor²⁴⁾ as well as exert an anti-apoptotic effect²⁵⁾. The clinical consequences arising from diurnal as well as short- and long-term gender differences in HRV, and whether the resiliency of the autonomic nervous system has salubrious or anti-aging effects warrants further exploration.

Table 4 Mean HRV parameters according to age and gender (Values are means $\pm$ SE. *: $p < 0.05$, **: $p < 0.01$ vs. Male by Student's *t*-test)

		20s	30s	40+
HR	Male	62.07 $\pm$ 1.44	65.33 $\pm$ 2.99	73.30 $\pm$ 2.16
	Female	73.89 $\pm$ 3.32**	72.46 $\pm$ 3.26	70.38 $\pm$ 2.82
SDNN	Male	85.91 $\pm$ 5.75	53.94 $\pm$ 6.18	37.54 $\pm$ 3.05
	Female	57.83 $\pm$ 5.52*	47.28 $\pm$ 4.68	42.54 $\pm$ 4.72
Ln TP	Male	8.39 $\pm$ 0.14	7.46 $\pm$ 0.31	6.37 $\pm$ 0.22
	Female	7.74 $\pm$ 0.26*	7.21 $\pm$ 0.23	6.98 $\pm$ 0.30
Ln LF	Male	7.30 $\pm$ 0.17	6.52 $\pm$ 0.39	5.36 $\pm$ 0.23
	Female	6.69 $\pm$ 0.36	5.82 $\pm$ 0.35	5.80 $\pm$ 0.32
Ln HF	Male	6.83 $\pm$ 0.17	5.75 $\pm$ 0.23	4.88 $\pm$ 0.28
	Female	6.27 $\pm$ 0.36	5.74 $\pm$ 0.38	5.05 $\pm$ 0.29
Ln LF/HF	Male	0.47 $\pm$ 0.17	0.77 $\pm$ 0.28	0.49 $\pm$ 0.23
	Female	0.42 $\pm$ 0.33	0.09 $\pm$ 0.33	0.75 $\pm$ 0.30

Overall

In general, autonomic and parasympathetic activities attenuate with age in men and women. A significant decline in overall autonomic and parasympathetic functions of men in their thirties may be associated with the feeling of sudden decrease in physical vitality after age 30. On the other hand, a more gradual decline in total autonomic and parasympathetic functions in women in later life may account for their greater longevity than men.

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