

Influence of age and gender on autonomic regulation of heart

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Abstract Heart rate variability (HRV) is a non-invasive method to measure cardiac autonomic function. Impairments in HRV have been proposed as independent risk factor for increased cardiac mortality and morbidity. Cardio protective phenomenon in females has been hypothesized to be due to differential autonomic tone. Age related loss of vagal control has been reported as predisposing factor for the development of cardiovascular disease. In this study we assessed effect of age and gender on autonomic regulation of heart in healthy volunteers. HRV data of 189 subjects (114 males and 75 females) were analyzed in time and frequency domains using customized program. Artifact free 5 min electrocardiogram segment was used for analysis. It was ensured that none of the subject had medical illness

such as diabetes, hypertension, thyroid disorders, cardiac disorders, diseases potentially related with autonomic neuropathy and major psychiatric illness by careful history and clinical examination. HRV recordings were done under standard laboratory condition. On correlation analysis SDNN, RMSSD, total power negatively correlated with age suggesting reduced autonomic regulation of heart with increase in age (SDNN: $r = -0.444$, $p < 0.01$; RMSSD: $r = -0.552$, $p < 0.01$; total power: $r = -0.474$, $p < 0.01$); similarly High frequency power (HF.nu) negatively correlated with age ($r = -0.167$, $p = 0.02$), denoting loss of vagal tone with aging. LF/HF ratio correlated positively with age ($r = 0.19$, $p < 0.01$) suggesting a relative increase of sympathetic activity with increase in age. On multiple regression analysis to control for effect of age and heart rate while comparing males and females, LF.nu showed significant reduction suggesting lower sympathetic tone in females ($\beta = -6.64$; $p < 0.01$) and HF.nu showed increase at trend level ($\beta = 4.47$; $p = 0.053$). In conclusion, there is overall reduction in autonomic control of heart with increase in the age. Sympathetic tone predominates and vagal tone diminishes with aging process. Females showed greater vagal tone than male. This differential autonomic tone indicate age, gender related predisposition to cardiovascular disease.

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1 Introduction

The autonomic nervous system is closely involved in the cardiovascular homeostasis. Very few studies have examined age related fluctuations of autonomic tone in healthy

individuals. These studies have shown that loss of vagal tone with aging process [1–4]. An understanding of the influence of age and gender on a cardiovascular regulation will provide insight into the autonomic physiology and might provide information of an individual susceptibility to the cardiac disease due to altered autonomic tone. An alteration in its function has strong implications in the pathophysiology of disease states like hypertension, myocardial ischemia. Heart rate variability (HRV) is a measure of regulation of cardiac function by the autonomic nervous system. HRV is a potential tool to assess and quantify physiologic, pharmacologic and pathologic changes in autonomic nervous system [5]. HRV is also used as a research tool in understanding cardiac neural regulation in various neurologic [6–9] and psychiatric disorders [10] and autonomic modulation following treatment [11, 12].

Several prospective studies have shown that impaired HRV predicts the incidence of cardiovascular disease [13, 14]. Decreased parasympathetic activity is linked with the cardiovascular mortality [15]. Studies have further explored the repercussions on HRV by disease pathologies like hypertension, obesity, family history, work stress and its potential association with a cardiac morbidity [15–17]. This makes it imperative to have a thorough understanding of the autonomic modulation in health, to quantify its alterations in disease states and to understand the underlying pathophysiology.

Most of the earlier work which studied the influence of age and gender on autonomic regulation of heart used 24-hour HRV recording. However, frequency domain measures are more accurate in short term HRV analysis [18]. In this study we assessed effect of age and gender on autonomic tone using short term HRV recording.

1.1 Methodology

Study was approved by the institutional ethics committee. The study was conducted in 189 healthy subjects (114 males and 75 females) after getting informed consent. Subjects were screened with a thorough history and clinical examination. Subjects with the history of use of medications that can alter HRV, use of nicotine, alcohol or any other illicit substances, diabetes, hypertension, thyroid disorders, history of any cardiac disorder, disease that is potentially related with autonomic neuropathy and psychiatric disorder were excluded from the study. All female subjects recording were done in proliferative phase of menstrual cycle. The test was conducted in the autonomic laboratory at National Institute of Mental Health and Neurosciences, Bangalore, India under standard conditions [10].

1.2 Data acquisition

An artifact free, lead II electrocardiogram (ECG) was recorded in all subjects at rest in supine position and

signals were conveyed through the analog digital converter (Power Lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1,024 Hz. The raw ECG was converted into consecutive RR intervals for analysis. The data was analyzed offline using an automatic programme that allows visual checking of the raw ECG and breathing signals. It was ensured that subjects breathed with a respiratory rate of 12–15 breaths/min [7, 10]. An error free 5 min ECG segment was taken for analysis and time and frequency domain parameters were calculated according to the Task force report on HRV [18]. Time domain parameters such as Standard deviation of RR intervals (SDNN) in milliseconds, Square root of the mean squared differences of successive intervals (RMSSD) in milliseconds and frequency domain parameters such as low frequency spectral power (LF) in ms^2 , high frequency spectral power (HF) in ms^2 also in high frequency normalized units (HF.nu), low frequency normalized units (LF.nu) and low frequency and high frequency ratio (LF/HF) were computed using customized software.

1.3 Statistical analysis

Correlation between HRV indices and age was made using Pearson correlation coefficient. Statistical significance was determined as $p < 0.05$. Multiple linear regression analysis was conducted to control for effect of age and heart rate while comparing males and females. In separate analysis HF.nu, LF.nu was selected as dependent variables with gender, heart rate, age as independent variables.

2 Results

Mean age of population was 33.7 years (male: 32.3 ± 11.2 , female: 35.8 ± 12.6 ; min age: 16 years, max age: 60 years). Table 1 shows the further details. On correlation analysis SDNN, RMSSD, total power negatively correlated with the age suggesting reduced autonomic tone of heart with increase in age (SDNN: $r = -0.444$, $p < 0.01$; RMSSD: $r = -0.552$, $p < 0.01$; Total power: $r = -0.474$, $p < 0.01$) (Fig. 1a–c); similarly HF.nu was negatively correlated with

Table 1 Age and gender characteristics of subjects

Age range (in years)	Number of male	Number of females
16–20	16	7
21–30	46	27
31–40	24	13
41–50	20	17
51–60	8	11
Total	114	75

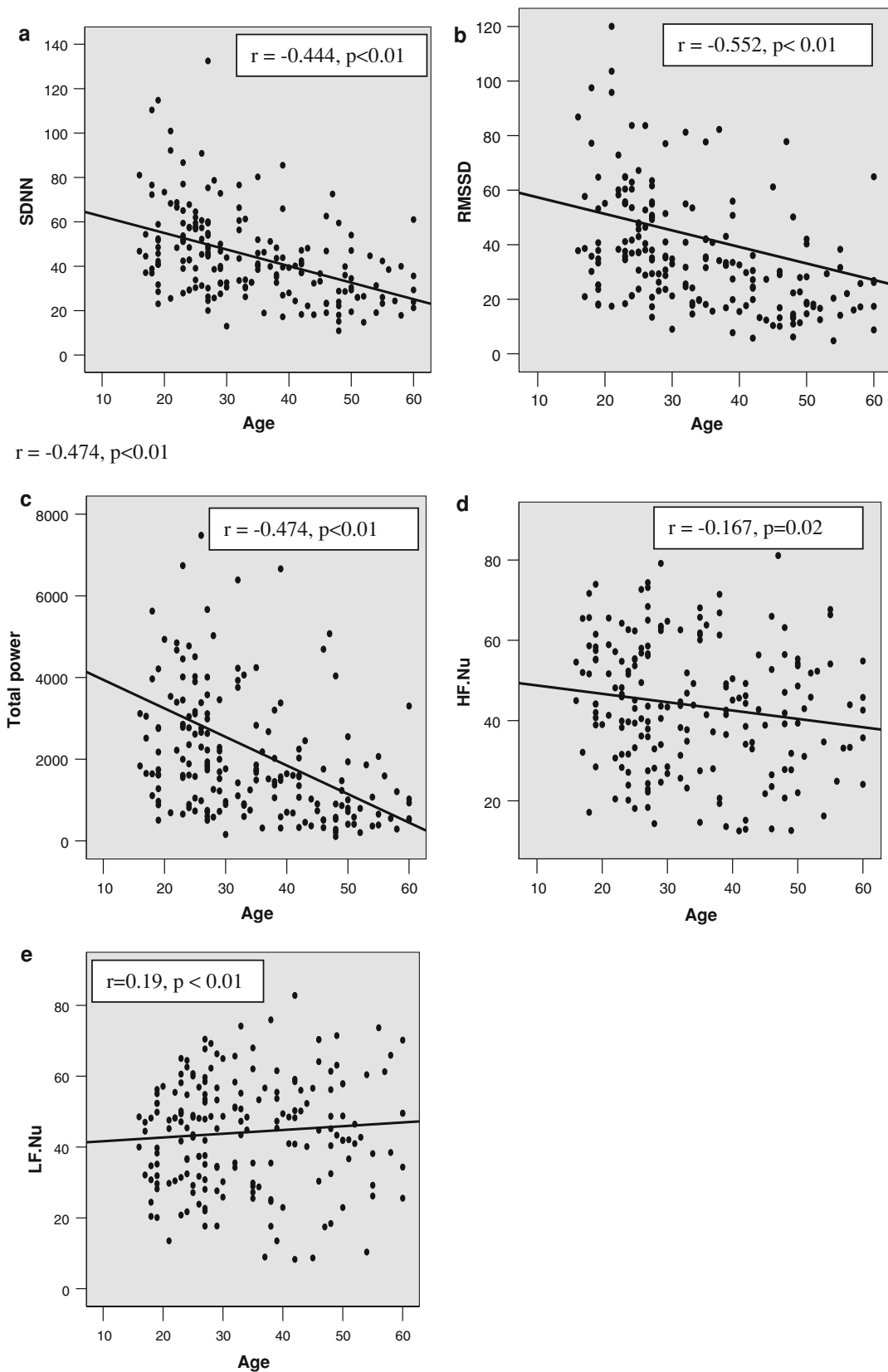


Fig. 1 X axis represents age and Y axis denotes HRV parameters Fig. 1a–e SDNN—standard deviation of average normal-to-normal R–R intervals RMSSD—square root of the mean of the sum of squares of differences between adjacent R–R intervals LFnu—low frequency normalized unit HFnu—high frequency normalized unit

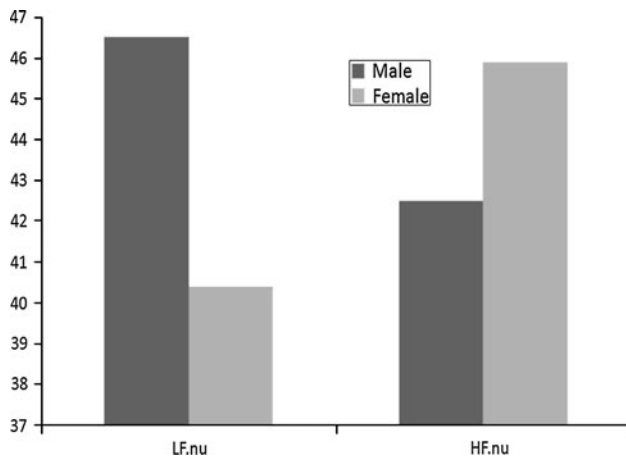


Fig. 2 Y axis denotes Low frequency normalized and High frequency normalized values. X axis Bar graphs for LF and HF nu for male and female group is indicated LFnu—low frequency normalized unit HFnu—high frequency normalized unit. Females showed more vagal tone (HF.nu = 45.86 ± 16.4) compared to males (HF.nu = 42.47 ± 15.3). Similarly, LF.nu was more in males compared to females (46.61 ± 15.17 vs 40.41 ± 14.95)

the age ($r = -0.167$, $p = 0.02$), (Fig. 1d) denoting loss of vagal tone with aging. LF/HF ratio correlated positively with the age ($r = 0.19$, $p < 0.01$) suggesting a relative increase of sympathetic activity with increase in age (Fig. 1e). Females showed more vagal tone (HF.nu = 45.86 ± 16.4) compared to males (HF.nu = 42.47 ± 15.3) however mean age of female group was more compared to male (35.7 ± 12.6 years vs 32.3 ± 11.3 years). On multiple regression analysis to control for effect of age and heart rate while comparing males and females LF.nu showed significant reduction suggesting lower sympathetic tone in females ($\beta = -6.64$; $p < 0.01$) and HF.nu showed increase at trend level ($\beta = 4.47$; $p = 0.053$) (Fig. 2).

3 Discussion

The present study explored the influence of age and gender on time and frequency domain measures of a cardiac autonomic function. We observed overall reduction in autonomic control of the heart with increase in age. Sympathetic tone predominates and vagal tone diminishes with the aging process. Females showed greater vagal tone than male.

In our sample, HF power was negatively correlated with the age which is consistent with earlier findings using both linear and non linear techniques suggesting an age related decrement in the functioning of parasympathetic nervous system [1, 2, 4, 19–22]. Similarly, our study is in line with earlier studies which showed sympathetic predominance with aging [23]. Most of the earlier work which studied the influence of age and gender on autonomic regulation of

heart used 24-hour HRV recording. However, frequency domain measures are more accurate in short term HRV analysis [18]. In this study we have replicated similar finding in short term HRV analysis. We have recruited subjects from 16 to 60 years. Since representative samples from all age group were included in study we believe that autonomic regulation changes reflected in the study is reproducible.

The literature about 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 down regulated [24]. Vagal terminals and axons in cardiac ganglia will degenerate with the aging process [25]. Thus it is notable that sympathetic and parasympathetic modulations of HRV appear to have different patterns in response to aging. Our study adds to the literature on sympathetic predominance and vagal tone loss as a part of aging process. Further studies about the structural changes that occur at the receptor level, the afferent and efferent pathway as well as the changes in the central nervous system, particularly the cardiac autonomic network with age might be able to throw light into the probable mechanisms behind the changes in HRV.

We observed increased parasympathetic activity in women, as reflected by a high HF.nu component. Earlier studies using 24-hour HRV demonstrated significantly higher vagal tone in females compared to male [3] The modulation of autonomic functions by the reproductive hormones especially estrogen has been postulated to be the reason behind the increased parasympathetic function. It has been shown that estrogen facilitates vagal control of the heart [26]. Neurons with estrogen receptors have been identified in the areas involved in the central autonomic network. Further, the anti-apoptotic role of estrogen on vascular endothelium and cardiac myocytes as well as the role of sex hormones in synthesis and release of neurotransmitters may act as possible mechanisms for the above effect. Recent studies suggest that differential cytokine expression also play a role in the gender difference in autonomic modulation. O'Connor et.al has shown a positive association between vagal tone and IL-6. The differential interaction between the immune and autonomic system resulting in different level of cardiac inflammatory pattern and a greater vagal tone in females compared to male population might be affording a better cardioprotection in the females [27]. In contrast males showed higher sympathetic tone which can be partly explained by increased number of neurons in the sympathetic ganglion and high muscular sympathetic activity [28, 29].

Limitations of present studies were as, we did not assess the physical activity of the subjects and no laboratory investigation was conducted before considering subjects as normal. However careful history and examination was

conducted before recruiting the subjects. Also, the gender effects could have been more substantiated if the hormonal levels could have been assayed and correlated with the HRV parameters. We did not assess nutrition status of the participants. Nutritional status might have influence on the autonomic tone. Further studies should address this issue.

In conclusion, there was a decrease in the autonomic functions with increase in the age. The reduction was more for the vagal tone shifting the sympathovagal balance to a relative sympathetic prominent state with the aging process. The parasympathetic autonomic functions were greater in the female population of reproductive age than the males which might account for greater cardio-protection in females.

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