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Research Article

Time-Frequency Spectral Analysis of Heart Rate Variability (HRV) in Large Populations in Correlation to Age and Gender

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Abstract

Heart rate variability (HRV) refers to the phenomenon of sinus heart rate changing periodically over a specific period of time. As individuals age, HRV changes, and elucidating the intrinsic connection between HRV and age serves an important reference for human health assessment and clinical diagnosis of cardiovascular diseases. This paper focuses on the correlation between HRV characteristics, including Heart Rate Average at rest, rmsSD, SDNN, LF, HF, LF / HF, Total Power, Autonomic Tone and others, and age in large populations, and then apply the results of the correlation analysis to age assessment.

Keywords: Time frequency analysis, Heart rate, Spectral analysis

Introduction

Heart rate variability (HRV) is defined as the periodic change in sinus heart rate over a specified time interval, which is characterized by the minor discrepancy between the initial and subsequent heartbeat cycles [1,2]. In recent years, a growing number of studies have confirmed the close relationship between autonomic nervous system activity and the development of cardiovascular disease [3,4]. HRV represents an indirect method for assessing the activity of the autonomic nervous system, and has been identified as a marker of cardiovascular risk [5,6]. The initial discovery of the use of HRV in the context of cardiovascular disease was made by in the early 1970 [7-9]. Their findings indicated that a reduction in HRV in patients who had experienced a myocardial infarction often preceded a higher mortality rate [10]. Currently, HRV can be monitored outside the hospital using portable electrocardiographic devices or wearable electrocardiographic sensors [11]. HRV can be employed to reflect the balance between the sympathetic and para sympathetic nervous systems, as well as their respective effects on cardiovascular activity. Furthermore, HRV is currently regarded as the most effective approach for evaluating the functional status of the human autonomic nervous system, given its non-invasive, rapid, and quantifiable advantages [12]. Consequently, HRV is an effective approach to detecting organic cardiac pathologies, including heart failure, coronary artery disease, and other related conditions. Given these advantages, it is now widely recognized that HRV is the optimal method for assessing the functional status of the human autonomic nervous system [13].

With the progression of age, a multitude of organic cardiac lesions may become discernible. It is therefore imperative to assess the relationship between HRV and age in order to facilitate the prediction of cardiac pathology. It has been demonstrated that HRV undergoes changes with advancing age. This equilibrium between HRV and the activity of the sympathetic and parasympathetic nerves is progressively disrupted, which is manifested in the autonomic nervous system by a decrease in its overall activity and a weakening of its regulatory capacity [14]. Furthermore, a negative correlation has been identified between the reduction in HRV and the prevalence of cardiovascular disease, as well as mortality. To ascertain whether the alteration in HRV is a typical consequence of the aging process or is attributable to other factors, such as disease, it is essential to elucidate the intrinsic relationship between HRV and age.

A detailed analysis of the correlation between HRV and age, and the clarification of the correlation between the two, provides a theoretical basis for researching and exploring the status of autonomic function in the elderly in clinical medicine. Furthermore, it provides a theoretical basis for further diagnosis and prevention of other diseases, enabling doctors to pay attention to the status of autonomic function in a timely manner and monitor the condition of autonomic function in a targeted manner. This allows for the implementation of effective interventions. Conversely, it elucidates the correlation between HRV and age. Conversely, the correlation between HRV and age has been elucidated, and HRV can be employed to assess the biological age of the body and to evaluate the health status of the human body.

It is therefore necessary to study the inter-correlation and influence relationship between HRV and age by conducting the study on a sufficiently large sample of healthy subjects. In this paper, we aim to adopt this research perspective and investigate the correlation between HRV time-domain features, frequency-domain features, and nonlinear features and age in a healthy population. Furthermore, we intend to apply one of the HRV features that exhibits a correlation with age to the evaluation of age.

Materials and Methods

All data were obtained from an accessible database within Medeia Inc. (Santa Barbara, CA). This study was supported by an external IRB review and approval (Argus, Scottsdale AZ, 2023-01) Patients records were obtained and categorized into different age groups. The age groups were further divided into male and female, and the RR interval (RRI) was taken for each patient separately. The relationship between the different genders in each age group and HRV was then analyzed.

The linear characteristics of HRV encompass both time domain indicators and frequency domain analysis indicators. Time domain indicators include the following:

SDNN: The standard deviation of all normal-to-normal (NN) intervals. This indicator suggests the degree of sympathetic activity. The normal value is (141±39) ms. A lower value suggests that sympathetic activity is increased, and the body's ability to adapt to the external environment is weakened.

rMSSD: The root mean square of the difference between adjacent NN intervals. This indicator reflects the degree of vagal activity. The normal value is (27±12) ms.

The frequency domain analysis indexes of HRV include:

Total power (TP): This reflects the overall activity of the sympathetic nervous system and assesses the regulatory ability of the autonomic nervous system.

High frequency (HF) (0.15～0.40 Hz): a good indicator for evaluating the function of vagus nerve, affected by the depth of respiration.

Low frequency (LF) (0.04～0.15 Hz): controlled by sympathetic-vagal nervous system, some studies believe that it is affected by sympathetic nerves, and can be used as a reliable indicator to reflect the sympathetic activity of the heart, and is affected by the vascular pressure-regulating reflex.

The **LF/HF ratio**: is an indicator of changes in the balance of sympathetic-vagal tone.

For the RRI series of each age group, time-domain metrics and frequency-domain analysis metrics were calculated. The computed results were expressed as mean±standard deviation. The statistical analyses were conducted using SPSS 26.0 (SPSS Inc., Chicago, USA), and significant differences between the tested indicators were deemed to exist at a probability level of $P < 0.05$.

Experimental Results

A total of 330,529 adult subjects (136,204 male subjects and 194,325 female subjects, aged 20-90 years) with RRI sequences were included in the database review providing a robust sample size for HRV analysis across different age and gender groups. The patients were categorized into 10 age groups: 20≤y≤25, n=5690; 25<y≤30, n=9820; 30<y≤35, n=15203; 35<y≤40, n=19000; 40<y≤45, n=24749; 45<y≤50, n=30779; 50<y≤65, n=38266; 60<y≤70, n=88787.

The detailed results from male subjects in this study, mean +/- standard error of the mean are presented in (Table 1) with the data shows the breakdown by age categories comparing average heart rate, rmsSDm/ ms, SDNN/ms, Total power, LF and HF and the ratio or LF/HF and the autonomic tone in the male subjects. There is a generalized trend to over time to observe a decrease from the initial values in the 20-25 year age group to the 80-90 age group in the parameters evaluated in this table. The data is also presented in (Figures 1-8) of this manuscript in a graphic description that details the changes over age that occur.

(Table 2) is similar to (Table 1) but (Table 2) is the detailed results from female subjects in this study, mean +/- standard error of the mean, with the data shows the breakdown by age categories comparing average heart rate, rmsSDm/ ms, SDNN/ms, Total power, LF and HF and the ratio or LF/HF and the autonomic tone in the female subjects. In our data analysis, there are both age and gender related differences and a a generalized trend to over time to observe a decrease from the initial values in the youngest group at 20-25 year age group to the oldest group at 80-90 age group in the parameters evaluated in this table.

Table 1: HRV differences by age in male subjects.

Indicator/Age	20 ≤ y ≤ 25, n = 2209	25 < y ≤ 30, n = 3718	30 < y ≤ 35, n = 6165	35 < y ≤ 40, n = 7717	40 < y ≤ 45, n = 9916	45 < y ≤ 50, n = 12655	50 < y ≤ 65, n = 15691	60 < y ≤ 70, n = 37698	70 < y ≤ 80, n = 31124	80 < y ≤ 90, n = 9811
Heart Rate Average (at Rest)	80.48 ± 12.62	78.67 ± 12.68	77.44 ± 11.90	76.51 ± 11.92	75.20 ± 11.64	74.39 ± 11.60	73.30 ± 11.33	71.22 ± 11.60	68.42 ± 10.80	66.56 ± 10.39
rmsSD / ms	31.69 ± 13.28	30.79 ± 12.99	28.88 ± 12.3	27.09 ± 12.3	25.67 ± 12.05	24.27 ± 11.6	23.05 ± 11.26	22.2 ± 10.81	21.72 ± 10.4	21.65 ± 10.18
SDNN / ms	48.54 ± 17.83	48.58 ± 17.38	45.19 ± 16.55	43.57 ± 16.6	41.93 ± 16.26	39.8 ± 15.88	37.74 ± 15.74	35.77 ± 15	33.81 ± 14.58	32.55 ± 14
Total Power	2520 ± 1998	2487 ± 1837	2135 ± 1634	1960 ± 1583	1802 ± 1526	1593 ± 1404	1418 ± 1523	1209 ± 1145	1022 ± 1038	899 ± 899
LF	758 ± 713	800 ± 743	687 ± 720	637 ± 697	563 ± 621	479 ± 559	399 ± 498	305 ± 387	226 ± 311	179 ± 262
HF	342 ± 317	298 ± 280	258 ± 260	218 ± 238	193 ± 228	168 ± 202	148 ± 185	133 ± 172	120 ± 152	115 ± 143
LF / HF	3.706 ± 4.438	4.528 ± 5.827	4.702 ± 7.096	5.108 ± 7.481	5.356 ± 7.98	5.107 ± 7.423	4.657 ± 6.767	4.031 ± 6.235	3.137 ± 4.942	2.422 ± 3.493
Autonomic Tone	70.37 ± 13.46	69.57 ± 13.08	65.88 ± 13.99	63.53 ± 14.37	61.24 ± 14.6	58.63 ± 16.43	54.49 ± 14.87	50.02 ± 14.93	44.93 ± 15.73	41.41 ± 16.42

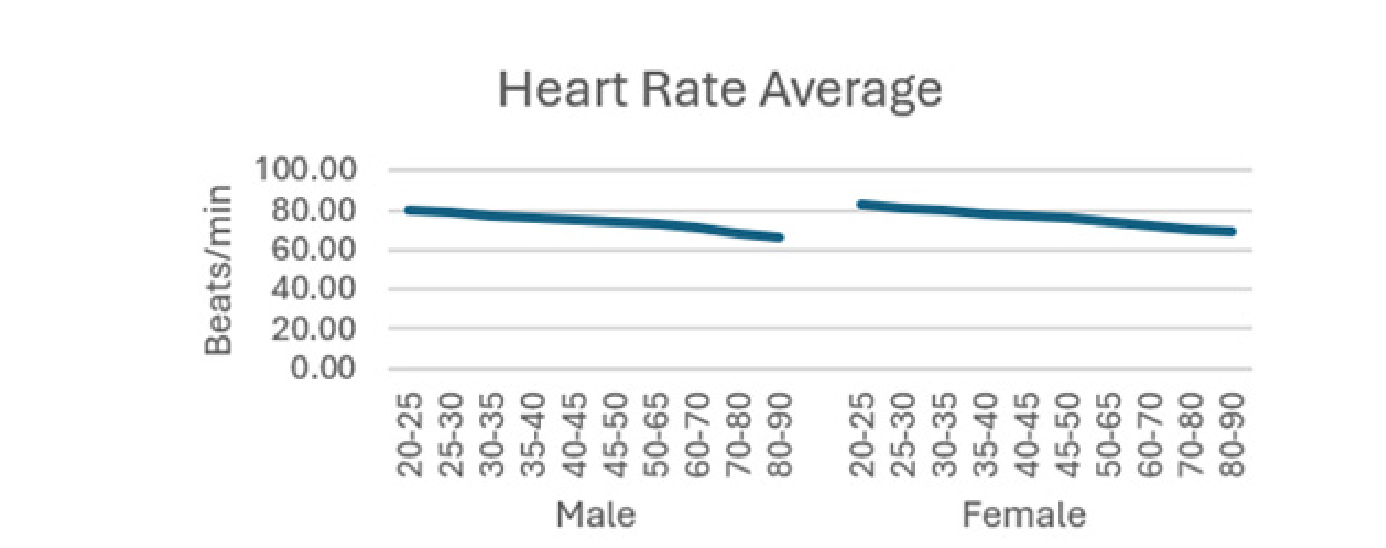

Figure 1: Heart rate average (at rest) in different age groups.

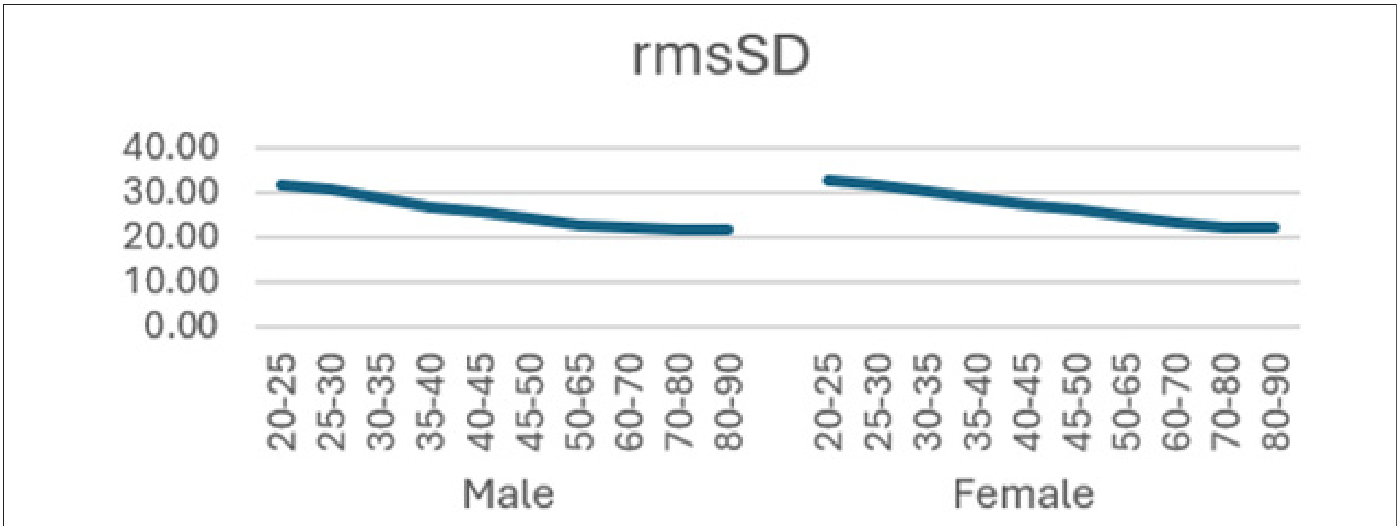

Figure 2: rmsSD in different age groups.

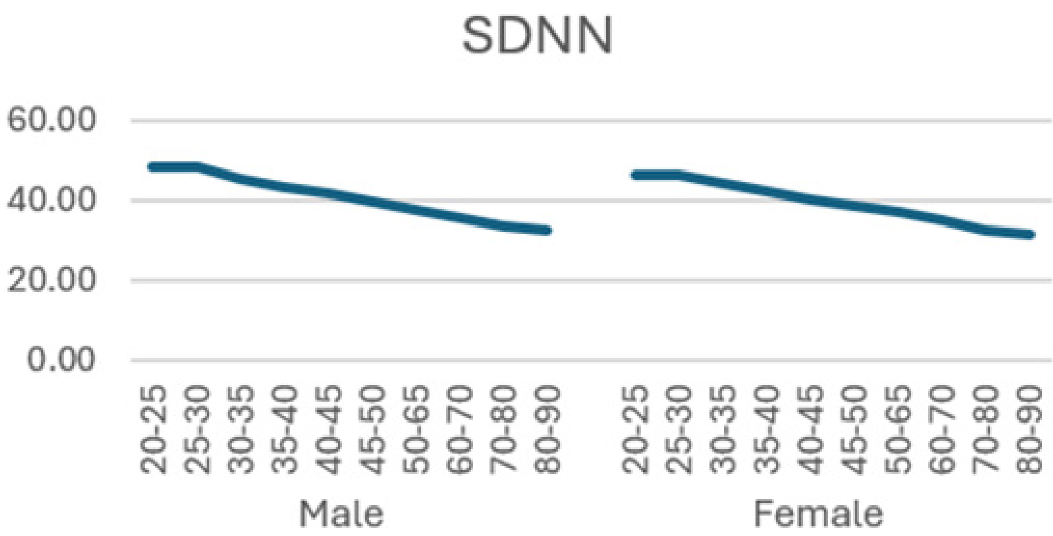

Figure 3: SDNN in different age groups.

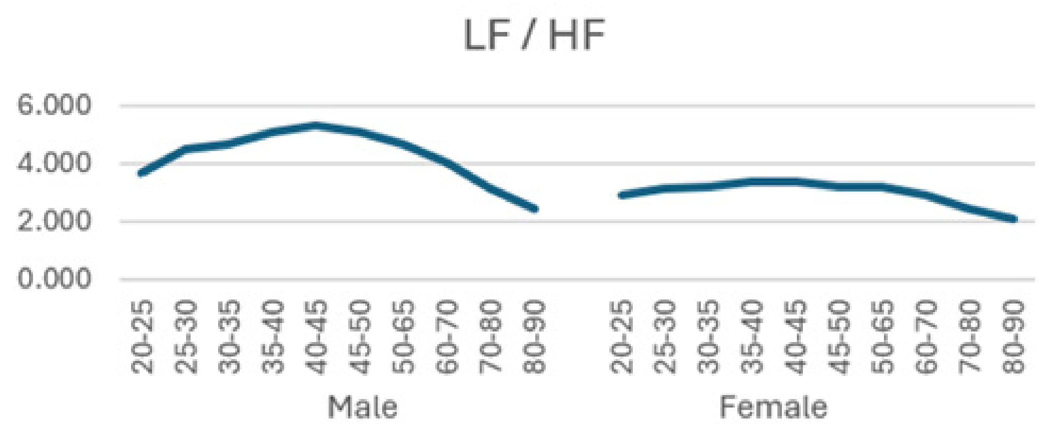

Figure 4: LF/HF in different age groups.

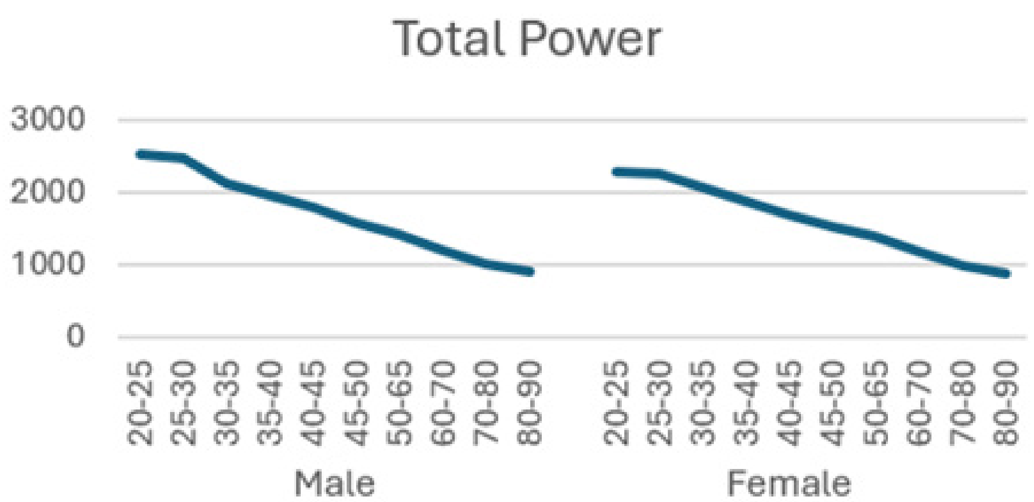

Figure 5: Total power in different age groups.

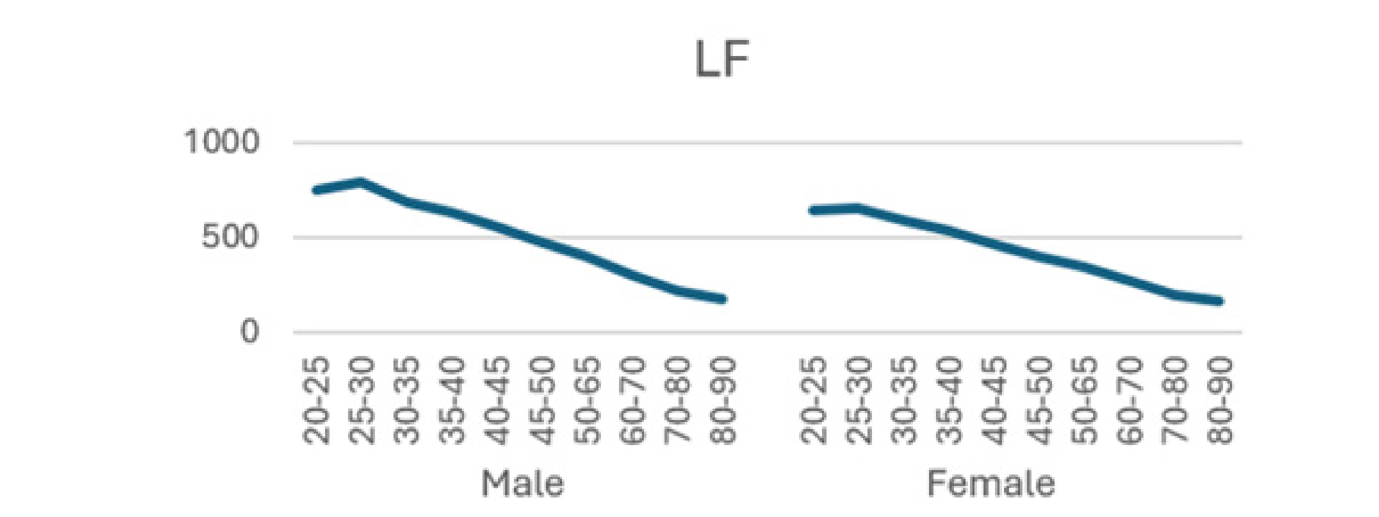

Figure 6: LF in different age groups.

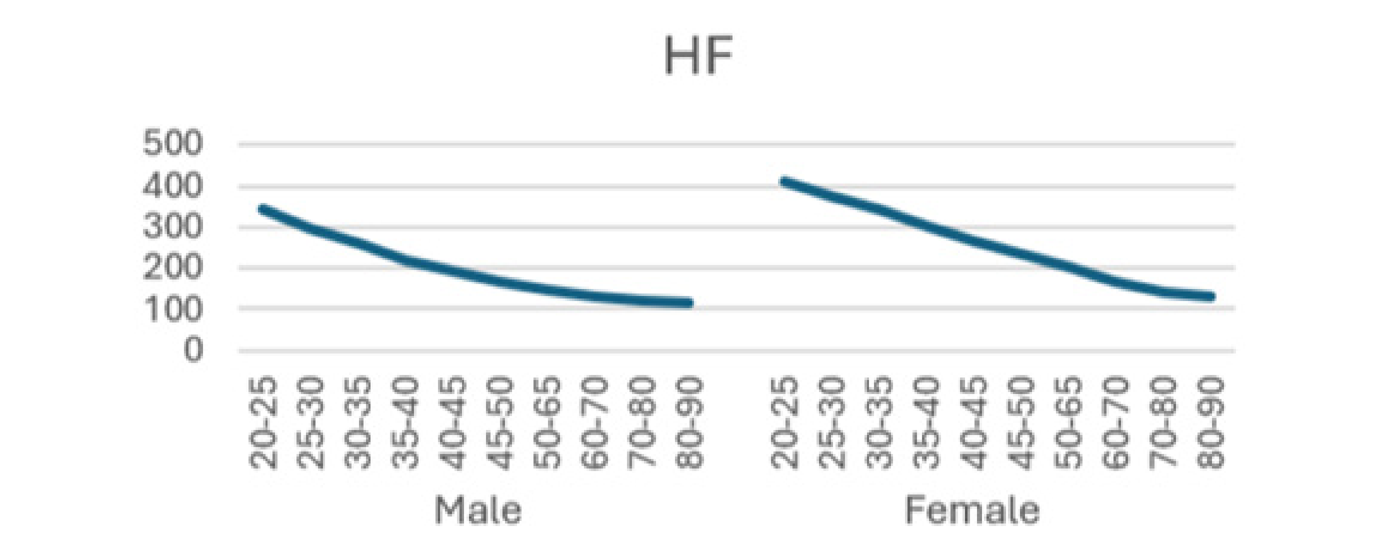

Figure 7: HF in different age groups.

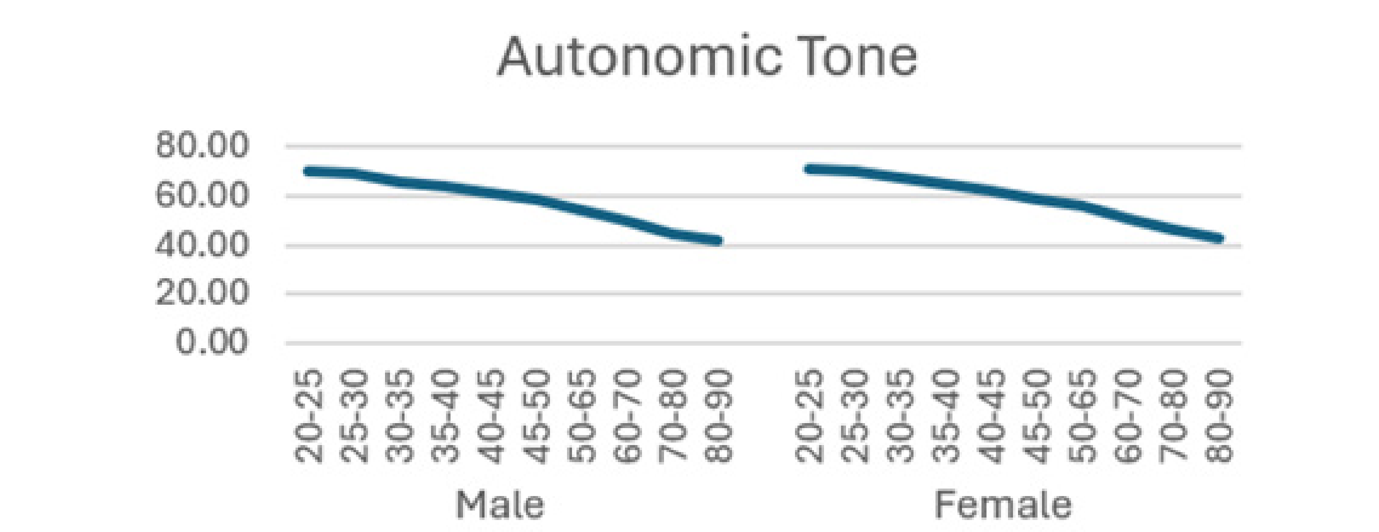

Figure 8: Autonomic tone in different age groups.

Table 2: HRV differences by age in male subjects.

Indicator/Age	20 ≤ y ≤ 25, n = 3481	25 < y ≤ 30, n = 6102	30 < y ≤ 35, n = 9038	35 < y ≤ 40, n = 11283	40 < y ≤ 45, n = 14833	45 < y ≤ 50, n = 18124	50 < y ≤ 65, n = 22575	60 < y ≤ 70, n = 51089	70 < y ≤ 80, n = 43517	80 < y ≤ 90, n = 14283
Heart Rate Average (at Rest)	82.48 ± 12.19	80.51 ± 11.47	77.44 ± 11.90	79.94 ± 11.43	77.36 ± 10.94	75.77 ± 10.78	74.34 ± 10.62	72.45 ± 10.57	70.45 ± 10.22	68.78 ± 10.06
rmsSD / ms	32.6 ± 13.87	31.92 ± 13.26	30.41 ± 13.27	29.09 ± 13.4	27.29 ± 13.04	24.27 ± 11.6	23.05 ± 11.26	22.2 ± 10.81	21.72 ± 10.4	21.65 ± 10.18
SDNN / ms	46.46 ± 15.81	46.43 ± 15.8	44.46 ± 15.7	42.52 ± 15.59	40.34 ± 15.65	38.79 ± 15.49	37.06 ± 14.93	35 ± 14.47	32.8 ± 13.9	31.67 ± 13.48
Total Power	2281 ± 1585	2249 ± 1590	2065 ± 1541	1883 ± 1456	1687 ± 1409	1538 ± 1569	1381 ± 1275	1183 ± 1129	984 ± 977	886 ± 888
LF	645 ± 645	655 ± 675	595 ± 629	537 ± 601	462 ± 542	401 ± 509	349 ± 464	271 ± 349	204 ± 269	171 ± 233
HF	412 ± 397	376 ± 363	344 ± 346	303 ± 326	265 ± 301	233 ± 272	201 ± 241	168 ± 208	141 ± 177	131 ± 164
LF / HF	2.886 ± 3.963	3.172 ± 4.88	3.189 ± 4.788	3.365 ± 5.352	3.375 ± 5.306	3.229 ± 5.025	3.195 ± 5.048	2.917 ± 4.564	2.46 ± 3.653	2.066 ± 2.794
Autonomic Tone	70.6 ± 12.2	69.73 ± 13.84	67.67 ± 13.66	64.92 ± 14.59	61.77 ± 14.37	58.7 ± 14.65	55.51 ± 14.53	51.06 ± 14.98	46.13 ± 15.45	43.01 ± 16.2

Additionally, (Figures 1-8) depict the graphical distribution of each HRV metric across the different age groups. Specifically, LF/HF demonstrated a pattern of initial increase followed by decline with age. Other indicators, including HRV, rmsSD, SDNN, total power, LF, HF, and autonomic tones, all exhibited a negative correlation with age, indicating a general decline in heart rate variability as individuals age. Additionally, the indicators demonstrated variability across gender groups, with males and females showing different patterns in HRV metrics.

Discussion

This study represents an effort to analyze data from a large cohort of patients undergoing heart rate evaluation in a 3rd party external IBB approved study. Heart rate variability (HRV) serves as an indirect indicator of the dynamic regulation of cardiac activity by the autonomic nervous system. Abnormalities in HRV are often indicative of abnormalities in vagal and sympathetic nerve function. In recent years, there has been a growing interest among scholars and professional societies in the field of cardiology in studying HRV. This is because HRV is now recognized as a common quantitative index for determining the function of autonomic activity. Furthermore, changes in its value are important indicators of cardiovascular dysregulation [14] and various other clinical conditions.

HRV encompasses data such as heart rate average (at rest), SDNN and RMSSD, all of which may manifest fluctuations with age, exhibiting regular changes. A substantial body of research exists on the relationship between age and HRV. For example, Voss and colleagues investigated the association between short-term heart rate variability and age in a cohort of healthy individuals. To this end, they calculated 5-minute linear and nonlinear HRV characteristics for 1906 healthy samples from the KORA S4 database. Furthermore, they investigated the development of HRV characteristics by age (25-34, 35-44, 45-54, 55-64, and 65-74 years). The results of this study demonstrated that the majority of short-term HRV characteristics exhibited significant intergroup variability [12]. In 2018, Estevez-Baez *et al*. evaluated the impact of age, gender, and heart rate on HRV characteristics in 255 healthy adolescents, categorized into two groups (13-16 and 17-20 years old) and two groups of healthy young adults (21-24 and 25-30 years old). This was achieved through experimental calculation of time, frequency, and information domains of HRV, with changes in HRV characteristics modelled using multiple linear regression models to adjust for the effects of heart rate, age, and gender. The findings indicated a tendency for HRV eigenvalues to decrease with age [13]. In general, there was a negative correlation between age and HRV eigenvalues. Additionally, Abhishekh *et al*. analyzed data from 189 subjects and found that SDNN, RMSSD, and total power were negatively correlated with age, indicating a decline in autonomic regulation of the heart as age increases [18]. Conversely, the LF/HF ratio showed a positive correlation with age, suggesting a relative increase in sympathetic activity. The study concluded that overall autonomic control of the heart decreases with aging, and females exhibited greater vagal tone compared to males.

In this study, the RRI sequences of 33,0529 subjects in the database were analyzed to obtain their HRV indicators, including rMSSD, SDNN, LF, HF, LF/HF and others. The study revealed that all the indicators exhibited a correlation with gender and a negative correlation with age, with the exception of LF/HF, which demonstrated a pattern of initial increase followed by a decline with age.

RMSSD

RMSSD is obtained by first calculating the time difference (in milliseconds) between each successive heartbeat, then squaring each value and averaging the results, and then taking the square root of the total. This process captures the beat-to-beat variability of the heart rate and is able to reflect the activity of the vagus nerve [15,16]. Most studies have shown a negative correlation between rMSSD and age [17], although *Glaucylara, et al*. showed a U-shaped change in rMSSD with age [18]. A study concluded that higher RMSSD in COVID-19 patients is linked to lower inflammation levels, a reduced need for treatment, and a shorter hospital stay [23]. Another study found that patients with diabetes and arterial stiffness had lower RMSSD, which is associated with a worse cardiovascular risk profile. These findings suggest that RMSSD is correlated with positive clinical outcomes [26]. Our results demonstrated a declining trend in rMSSD with age, with a more pronounced decline observed in females. This suggests a reduction in vagal mobility of HRV with age, indicating a loss of cardiovascular system variability during the natural aging process.

SDNN

The standard deviation of the normalized NN intervals (SDNN) is expressed in milliseconds [15]. SDNN values can be used to predict the morbidity and mortality associated with heart disease. They are negatively correlated with heart risk, whereby values above 100 ms indicate a healthy state, while values below 50 ms are indicative of an unhealthy state [19,20,26] study showed that SDNN decreased linearly with age in 553 healthy participants, with males exhibiting significantly higher values than females [22]. In a study conducted by Beckers *et al*., 24-hour electrocardiogram (ECG) signals were recorded from 276 healthy subjects aged 18 to 71 years. The findings indicated a decline in SDNN values with advancing age [27]. The results align with our study, demonstrated that SDNN values were slightly lower in women than in men and exhibited a progressive decline with age, indicating an incremental increase in the risk of cardiovascular disease in the elderly.

LF/HF

Low frequency (LF) corresponds to variability in the frequency range of 0.04 Hz to 0.15 Hz and is primarily regulated by the sympathetic nervous system. The LF component of the spectrum is indicative of the sympathetic regulation of heart rate variability and is associated with stress and mood in vivo. It primarily reflects stress receptor activity at rest [26]. In contrast, high frequency (HF) corresponds to variability in the frequency range of 0.15 to 0.40 Hz and is reflective of parasympathetic activity [25]. A reduction in HF typically indicates a deterioration in cardiovascular health, which may be indicative of an increased risk of cardiovascular disease [24]. The LF/HF ratio is a measure of the relative activity levels of the sympathetic and parasympathetic nervous systems. Higher values indicate increased sympathetic activity, whereas lower values imply a predominance of parasympathetic activity. This is a sensitive predictor of arrhythmia, and changes in values often imply an unstable electrical activity of the heart. Our results demonstrated a decline in both LF and HF with age, accompanied by an initial increase and subsequent decline in LF/HF, exhibiting an "n" pattern. It seems reasonable to posit that middle-aged individuals are more susceptible to autonomic nervous system dysfunction as a consequence of the elevated LF/HF ratio, which may be attributed to the persistent sympathetic hyperactivity induced by their fast-paced occupational circumstances [27-32].

Limitation

The limitations of this study include a retrospective and non-randomized design. Future prospective randomized controlled trials are needed to validate these observations.

Conclusion

This study represents a large data set collected over several years in patients. We performed an external IRB reviewed and approved study of the data. The HRV indices which we evaluated included heart rate, rmsSD, SDNN, total power, and LF and HF including the ratio of LF/HF, demonstrate a correlation with age, exhibiting either an increase or a decrease with advancing age. This trend highlights the potential of HRV as a valuable tool in understanding the physiological changes that occur with aging. Additionally, gender differences in HRV indices suggest that both age and sex play crucial roles in shaping heart rate variability patterns. As such, HRV analysis may offer important insights into cardiovascular health as well as other conditions and can be used as a non-invasive means to assess the likelihood of developing heart and other diseases. We separated out the male from female values for the HRV parameters in this evaluation.

Further research is warranted to refine the application of HRV metrics in predicting heart disease risk, considering the combined effects of age, gender, and other contributing factors.

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