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Review

Heart Rate Dynamics and Its Role in Aging and Lifespan

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ABSTRACT

In mammals, heart rates vary depending on the species. There are also such differences between species. The level of heart rate can lead to discussions about longevity between humans and other species. This is an important factor in the development of medicines or other treatments. Studies have been carried out to help living beings live longer and healthier lives. In this review, we will examine the longevity correlates of heart rate and the differences between species, together with the results of pharmaceutical experiments.

Keywords: Digoxin, heart rate variability, ivabradine, myocardial infarction, resting heart rate

As humans, solving our cardiovascular problems may be important for extending our lifespan. According to many studies and observational evidence, resting heart rate (RHR) has been found to inversely correlate with lifespan in mammals, which is responsible for maintaining internal balance.[1]

In mammals, heart rate also serves as an indicator of cardiac autonomic nervous system (sympathetic and parasympathetic) activity and metabolic rate. Resting heart rate is known to be a fundamental characteristic. Many studies have examined the effects of various heart rate-lowering drugs, such as beta-blockers and selective sinus node inhibition, on the cardiovascular system.[2]

With scientific advances, questions have been asked about genetic factors related to RHR, as well as whether high RHR is a risk factor or risk marker. In addition, digital health data can be collected more quickly with some algorithms, cell phone applications, and similar systems.[3] This is also an increasingly important issue for the public. In addition, significant differences in RHR have been found within species. For example, large-sized animals such as whales and elephants have an RHR of approximately 30-35 beats per minute (bpm), whereas in mice it can be as high as 600-700 bpm.[4] However, mammals with a lower average RHR tend to live longer lives than those with a faster RHR.[5]

THE IMPORTANCE OF RESTING HEART RATE

The normal limits of RHR, known as the value of heart rate measured at rest, are generally considered to be between 50 and 90 bpm.[6] The US National Health and Nutrition Examination Survey, a study conducted between 1999 and 2008, assessed the distribution of RHR in more than 35,000 people without cardiovascular disease. This study showed that the mean heart rate in men over 40 years of age was 71 bpm, with the 2.5th percentile at 49 bpm and the 97.5th percentile at 95 bpm.[7] Similarly, the mean RHR in women over 40 years of age was 73 bpm, with a 95th percentile range of 53-97 bpm. In general, it appears that RHR differs depending on gender as women tend to have higher heart rates compared to men. Among participants over 40 years of age, RHR is similar across age groups,[3] and this similarity persists even at older ages.[8] However, it should be noted that a given heart rate may be within the reference range but still be considered harmful. For example, the 2017 American College of Cardiology/American Heart

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Association guidelines for hypertension recommend that 63% of the population aged 45 to 75 years is eligible for anti-hypertensive therapy.[9]

Observations on Heart Rate Reduction With Beta-blockers

Observational studies in patients with ischemic heart disease (IHD) show findings consistent with the results of randomized controlled trials. Studies of the use of 25 beta-blockers (21 with beta-blockers and four with calcium channel blockers) after myocardial infarction (MI) have shown a strong association with heart rate reduction and reduced risk.[10] Indeed, survival benefit is closely associated with a reduction in heart rate and not with a specific drug or beta-blocker dosage, but with a reduction in heart rate in general. These findings are consistent with the study conducted by Kjekshus.[11] In 1986, he found both a difference in infarct size and a reduction in mortality. Beta-blocker trials have also been associated with a reduction in heart rate. Furthermore, heart rate is a particularly important factor in patients with heart failure. Comprehensive heart rate reduction is particularly beneficial in patients with left ventricular heart failure.[12]

A meta-analysis of beta-blocker trials showed that the reduction in mortality was not related to beta-blocker dosage, but was related to the magnitude of the reduction in heart rate.[13] Furthermore, another meta-analysis of 35 trials showed that improvements in left ventricular ejection fraction were highly associated with changes in heart rate.[14]

Resting Heart Rate, Heart Rate, SDNN, and rMSSD

Resting heart rate is the primary marker for understanding an individual's overall physical condition. Rhythmic changes in heart rate at any given point reflect the complex interactions between the parasympathetic and sympathetic nervous systems.[15]

Assessing workload through heart rate variability (HRV) can be confusing unless RHR is known. Resting heart rate and HRV are also important for athletes to justify training load, recovery, and adaptation. A study was conducted to investigate the values of RHR and HRV parameters of cricketers, athletes, and non-athletes in West Bengal. Forty-three male volunteers with a mean age of 20.2 ± 2.1 years were selected for the study. Five-minute R-R intervals were recorded in the supine position at rest. The mean heart rate, standard deviation of all NN intervals (SDNN) and root mean square of successive differences (rMSSD) values of the cricketers were 57±5 bpm, 54.5±15.7 ms, and 66.8±21.6 ms, respectively. While there was no significant difference in the SDNN and rMSSD values of the three groups, a significant ($p<0.05$) difference was observed in the RHR values of the cricketers. Low RHR, a type of bradycardia, was found in cricketers.[16]

In one of the studies on heart rate deceleration, Zulfiqar et al.[17] calculated four standard 24-hour time-domain measures of heart rate variability by the decade in 344 healthy subjects aged 10 to 99 years. In this particular phase study, the researchers observed a significant increase in rMSSD and the percentage of consecutive normal-to-normal intervals differing by more than 50 milliseconds (pNN50) in 20 subjects aged 80 years. Together with these results, they concluded that this group is a sufficient explanation for longevity.

In some studies, it is generally accepted that the RHR remains unchanged in aging adults.[18] This may be in contrast to aging at the cardiovascular level, with progressive increases in systolic blood pressure, pulse pressure, pulse wave velocity, and left ventricular mass, and increased incidence of atrial fibrillation and coronary artery disease.[19] There is an ineffective response to beta-adrenergic stimuli and endothelium-mediated vasodilator compounds, with reproducible age-related declines in maximal heart rate, reflex responses to heart rate, and heart rate variability.[20]

Resting heart rate declines gradually from approximately 140 bpm in newborns to stabilize at adult levels of 50 to 90 bpm,[21,22] which is considered the normal level. In individuals aged 65 years and older, and particularly in individuals aged 85 years and older, the evidence on potential responses of RHR over time is inconclusive and there seems to be consensus that in the absence of pathology, RHR continues unchanged from early adult life. Data from the Framingham Study show that RHR continues to decline with advancing age, especially in the oldest old. The association between RHR and mortality rates among this group was found in adults with cardiovascular disease. Higher RHR values are associated with lower survival.[23,24]

A birth cohort study was conducted following individuals residing in Jerusalem (born between June 1920 and May 1921) until 1990. The methodology of the study has been reported in detail.[25,26] In Phase I (1990-1991, age 70), Phase II (1997-1998, age 78), and Phase III (2005-2006, age 85), data were processed

on 453, 856, and 1,044 participants, respectively. The Phase I study sample was replenished in Phases II and III with new participants randomly recruited from the same birth cohort. The representativeness of the study sample was confirmed by examining hospitalized patients' disease incidence, healthcare utilization, and mortality rates. In addition, there were no significant differences in comorbidity or subsequent mortality rates between subjects of the same age who joined the study later. Each participant or legal heir was informed and the Hadassah Hebrew University Medical Center institutional review board approved the study.[27]

A study was conducted using a specialized tool called the Omron 705IT device, which was employed by the researchers for their investigation. Omron 705IT is a medical device for measuring and monitoring blood pressure. This device is manufactured by Omron Healthcare. From an academic perspective, the importance of the Omron 705IT stems from the fact that blood pressure is an indicator of health status. Blood pressure is associated with the functionality of the cardiovascular system and can be a symptom of various health problems, such as hypertension (high blood pressure).[28]

Blood pressure measurements were made while sitting supported at arm's length and were performed accurately with an Omron 705IT electronic sphygmomanometer (Omron Corporation, Kyoto, Japan). These measurements were performed to determine blood pressure above 140 mmHg systolic or 90 mmHg diastolic, which is an important criterion for the diagnosis of hypertension and antihypertensive medication. This definition was determined in accordance with criteria used in widely accepted guidelines [e.g. The Eighth Joint National Committee (JNC-8) or European Society of Cardiology/European Society of Hypertension guidelines (ESC/ESH). During the course of the study, participants taking antihypertensive medication were classified as having hypertension. This indicates that antihypertensive medication is an effective treatment to regulate and control blood pressure.[29] The data shows that participants were recorded according to the classes of medicines used. For example, the use of different groups of medicines was taken into account, including medicines such as beta-blockers. The diagnosis of IHD was based on participants' history of previous hospitalization for MI or acute coronary syndrome, coronary angiography results indicating the presence of coronary artery disease,[30] electrocardiogram findings, typical symptoms of angina pectoris, and previous history of coronary revascularization. These criteria reflect commonly used standards to ensure a reliable diagnosis of IHD. The diagnosis of diabetes mellitus is based on a diagnosis made by a physician. This is an important step in controlling blood glucose levels and managing diabetes.[31] The diagnoses were accurately made by the doctor after medical assessment, system review, and examination. The disease diagnoses used in this study were standardized by the International Classification of Diseases, Ninth Revision.[32] This enables researchers to classify disease data in a consistent way and to obtain comparable results.

To assess their own health, the researchers asked the following question: "Compared to your peers, do you feel healthy?" This question was used as a measure to assess the functional status of individuals through six activities of daily living. Activities of daily living encompass a range of tasks like transferring, dressing, bathing, maintaining toilet hygiene, eating, and ensuring continence.[33] If individuals are dependent on another person for one or more of these activities, it is considered to have limited functional status.[34] The Mini-Mental State Examination was also administered. This test was used to assess cognitive functioning and to determine whether cognitive abilities were within the normal range.[35]

As expected, there was a significant increase in the incidence of cardiovascular disease and hypertension and the use of beta-blockers in the cohort over time. The mean RHR at ages 70, 78, and 85 years was 74.3±10.7, 73.1±11.2, and 65.2±10.5 bpm for men and 75.1±9.9, 74.5±10.9, and 68.6±10.5 bpm for women, respectively. The decline in RHR between 78 and 85 years of age was significant in both sexes ($p<.001$). Differences between sexes in RHR were significant at age 85 years ($p<.001$). The data show changes in RHR over time in survivors examined at all three time points. These findings confirm a decrease in RHR with aging in both sexes. Resting heart rate was consistently lower in those with IHD at all ages and also in those without diabetes mellitus. At 85 years of age, RHR was significantly lower in people who were highly educated, physically active, and independent in activities of daily living, with preserved cognitive function and a diagnosis of IHD or hypertension. Resting heart rate was consistently lower in beta-blocker users than in nonusers (68.8±9.3 vs 75.9±10.1 at 70 years; 67.8±9.7 vs 75.5±10.9 at 78 years; 62.1±9.0 vs 70.2±10.4 at 85 years, $p<.001$ at all ages). When examined as a continuous variable, RHR was significantly lower in 78-year-old women

who survived to age 70, in both sexes at age 78 who survived to age 85, and in 85-year-old men who survived to age 90. Similarly, when RHR was examined as a binary variable, Kaplan-Meier survival plots showed significantly greater survival associated with lower RPR in women aged 70-77 years, men aged 78-84 years, and both sexes aged 85-90 years.[27]

High Blood Pressure and Resting Heart Rate

A direct association between high blood pressure and high heart rate has been shown in both cross-sectional studies and prognostic studies.[36,37] For example, there are studies showing that in apparently healthy young individuals, those with high heart rates are more likely to develop hypertension.[38]

In the Coronary Artery Surgery Study registry, a study of 25,000 patients with suspected or proven coronary artery disease followed for 15 years, an RHR above 82 bpm was associated with a 32% increased risk of death compared to patients with a heart rate below 62 bpm.[39]

In patients with acute myocardial infarction, several studies have shown that elevated heart rate in the acute setting is associated with poor outcomes.[40] For example, in the US Global Registry of Acute Coronary Events registry, heart rate on admission was identified as one of the eight most important predictors of in-hospital mortality.[41] Similarly, in a contemporary European study, heart rate on admission was highly predictive of in-hospital mortality in patients with acute coronary syndrome in 58 hospitals.[42] In these studies, an admission heart rate above 80 bpm was associated with a three to five times greater risk of death than those with lower heart rates.

Impact of Physical Activities

Regular moderate to vigorous physical activity has been scientifically proven to reduce the risk of death due to many health problems such as all-cause mortality, cardiovascular mortality, death from cancer, stroke, heart disease, breast cancer, and colon cancer,[43] Endurance-oriented physical exercises can reduce RHR and improve the overall health profile. Endurance athletes are known to have higher parasympathetic tone and lower RHR compared to the general public.[44] Exercising significantly increases pulse rate while markedly reducing RHR and also reduces the total number of heartbeats over a 24-hour period.[45]

The autonomic nervous system function is clinically assessed by measures such as RHR, HRV, or pulse rate recovery after exercise.[46] Heart rate variability is influenced by many physiologic or pathologic conditions. Regulations due to sympathetic modulations are slow on the time scale of seconds, whereas parasympathetic modulations occur faster on the time scale of milliseconds. Therefore, parasympathetic influences cause faster changes in the beat-to-beat regulation of the heart.[47]

There is a large literature documenting a range of determinants that influence autonomic tone.[48,49] The Human pulse rate is irregular and varies over time.[50] This variability is thought to be the result of complex interactions between external environmental and behavioral factors and internal cardiovascular regulatory mechanisms (neural centers, neural reflexes, and humoral influences) that are not yet fully understood.[51] By measuring these variations, HRV helps us understand the complex regulations behind heart rate.[52]

These explanations emphasize the effects of endurance sports on heart rate and its relationship with the autonomic nervous system. Regular exercise decreases pulse rate and this has positive effects on overall health.

In order to assess the physical activity level of the individuals, the researchers asked the participants the question "How often are you physically active?". The answer options were (<four hours/week; regular physical activity, e.g. walking for one hour daily; vigorous sports activity at least twice a week, e.g. running, swimming).[27] Physical activity level was divided into two categories: sedentary (response 1) and physically active (responses two, three, or four). This four-item questionnaire was adapted from the Gothenburg population study involving participants over 70 years of age, and this cut-off point has been shown to predict mortality risk and functional decline in the current study cohort.[53] The questionnaire assessed current physical activity levels at the time of questioning and did not take into account previous activity levels. Assessment of physical activity level is an important parameter that has a significant impact on healthy aging and general health status.[54] The questionnaire used in this study shows an association between physical activity level and mortality risk and functional decline, in line with the Gothenburg population study. These results emphasize that low physical activity levels may contribute to health problems and functional limitations in the aging process. The survey's assessment of current physical activity levels may help us better understand the effects of physical activity on health outcomes, as it reflects participants' current activity habits.

Such an assessment may provide an important tool for healthcare providers to determine the physical activity levels of older individuals and provide appropriate health advice.

However, HRV is an index used as a marker of cardiac autonomic nervous function and is an indicator of imbalanced sympathetic/vagal activities (sympathetic tone increase and/or vagal tone depression).[55] Heart rate variability can independently predict cardiovascular disease mortality not only in individuals with certain diseases such as coronary artery disease or chronic heart failure but also in apparently healthy populations.[56,57]

There are many different methods for measuring HRV. Most clinicians may not be familiar with HRV indices and non-electrophysiologists are advised to refer to the data presented in the article by Soares-Miranda et al.[58] for a better description. In general, HRV is usually analyzed in the time or frequency domain. Time domain indices are mathematical calculations of consecutive RR intervals and are correlated with each other [SDNN, standard deviation of the averages of NN intervals for all 5-minute segments (SDANN), pNN50, etc.]. Frequency domain indices are more detailed and based on spectral analysis.[59] These indices are often used to assess the contribution of the autonomic nervous system [very-low frequency (VLF), low-frequency (LF), high-frequency (HF), HF/LF ratio]. Spectral analysis of heart rate signals provides the power spectrum density and shows the relative contribution (amplitude) of each frequency in a graph after applying the Fast Fourier transform to the raw signal.[60,61]

Statistical analyses were performed and results were presented with descriptive statistics, defined as the mean and standard deviation for normally distributed data. Percentages were calculated appropriately. Differences between means were evaluated using t-tests for continuous variables and chi-square tests for categorical variables. Kaplan-Meier survival curves were constructed and the log-rank test was used to examine RHR as a dichotomous variable (<or>80 bpm). The log-rank test is a statistical test used in survival analyses. This test is used to determine whether there is a statistically significant difference in survival times between two or more groups.[62]

Heart rate shows an inverse relationship with lifespan in all species, including humans.[63] In individuals with cardiovascular disease, a high heart rate has been associated with an increased risk of death, and such patients benefit by reducing heart rate through pharmacologic means.[64] However, the cause-and-effect relationship between heart rate and longevity in healthy individuals has not been conclusively established.[65] Therefore, a study in mice prospectively examined the effects of pharmacologically reducing heart rate throughout life on longevity.[2] In the study, C57BL6/J mice were given either a placebo or drinking water containing a drug called ivabradine for 12 weeks. The heart rate and body weight of the mice in the placebo or ivabradine group were monitored. According to the results of the study, ivabradine drug decreased heart rate by 14% (median, interquartile range 12-15%) and increased median life span by 6.2% (p=0.01). Similar studies also support this.[66] There were no significant differences in body weight and macroscopic findings between the placebo and ivabradine groups.[67] This study shows that reducing heart rate does not increase life span by the same amount, but it does provide a significant extension of 6.2%. These findings were obtained in healthy mice and no firm conclusions can be drawn about similar results in humans. However, this study could provide a basis for future research to understand the effects of heart rate on longevity and develop potential therapeutic strategies.[68]

EFFECT OF PHARMACEUTICAL STIMULI ON RESTING HEART RATE

Impact of Ivabradine on Cardiovascular Function

Ivabradine is a drug that acts on the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activated by hyperpolarization in the sinus node. [69] Unlike other drugs such as beta-blockers, calcium antagonists, or digoxin,[70-73] ivabradine does not affect blood pressure or ventricular function. However, ivabradine may block HCN channels that also act on cardiac structures and ventricular tissue outside the sinus node, which may lead to non-specific effects of the drug.[74] There may be other effects not related to HCN channels. This drug, compared with other drugs such as beta-blockers, calcium antagonists, or digoxin, has been observed to have no effect on blood pressure or ventricular function, either acutely in porcine models or after repeated administration in mice and humans.[75-78] However, HCN channels are also present in cardiac structures outside the sinus node, particularly in ventricular tissue with hypertrophy and failure,[79] and blocking these channels may lead to non-specific effects of ivabradine.[80,81] Furthermore, there may be

other pleiotropic effects not related to HCN channels outside the sinus node. In studies in pigs, ivabradine use was observed to reduce heart rate and infarct size, although this reduction was abolished by atrial pacing. In mice, ivabradine reduced the formation of reactive oxygen species. Therefore, a dose of ivabradine aimed at reducing the heart rate by 15% was used to prospectively study its effect on survival in mice.[76,77]

Digoxin and Resting Heart Rate

Studies in mice have shown that reducing heart rate by about 50% with a drug such as digoxin increased life expectancy by 20%.[82] However, this reduction was accompanied by a corresponding reduction in body weight.[83] Therefore, the role of other factors, such as caloric restriction, in influencing longevity should not be underestimated. Reducing heart rate without side effects is a difficult process even under experimental conditions and becomes even more difficult in long-term studies, especially where mortality is determined. Electrical or surgical ablation of the sinus node can cause trauma and damage longevity by increasing the risk of arrhythmias.[84] Therefore, ivabradine was preferred among pharmacologic methods.

In an important recent study, Gent et al.[2] reduced heart rate in mice using ivabradine compared to placebo by selectively inhibiting the sinus node. Mice treated with ivabradine had a 14% reduction in median heart rate and a 6% prolongation of median life expectancy compared to the placebo group. These results suggest that RHR may affect life expectancy as a modifiable determinant. The authors also estimated that the 6% increase in longevity caused by a 14% reduction in RHR could equate to a 5-year increase in lifespan in humans. Interestingly, these figures roughly correspond to observations from the Copenhagen City Heart Study, where a 19% lower heart rate (65 vs. 80 bpm) was associated with 4.6 years longer life expectancy in men and 3.6 years longer in women.[85]

In conclusion, changes in heart rate affect the lifespan of mammals, a finding supported by pharmaceutical experimentation and research. In particular, it has been observed that the increase in heart rate is inversely correlated with the lifespan of mammals. This suggests that the lifespan of mammals is significantly affected by heart rate. Although there are certain differences between sexes, it can be generally accepted that an increase in heart rate negatively affects lifespan. These findings also support that reducing heart rate with drugs such as beta-blockers has the potential to extend lifespan. Sports and exercise are also known to be associated with lower RHR. Therefore, it is possible to say that sport and exercise are directly proportional to longevity. Exercise can potentially extend lifespan by reducing the RHR in the body. However, it is observed that the RHR value decreases as we age, and this can be said to increase the body's chances of survival. However, many factors need to be taken into account when assessing this. For example, factors such as body size also play an important role. When making comparisons between different species, it's important to avoid directly juxtaposing humans with other organisms, as each species possesses distinct physiological characteristics and survival strategies. It is an academically supported idea that changes in heart rate affect the lifespan of mammals. Reducing heart rate, especially achieving a low RHR in combination with lifestyle factors such as sport and exercise, could potentially be associated with a longer lifespan. However, it is important to conduct more research on this topic and to conduct comprehensive studies on different species.

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