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Resting Heart Rate and its Effect on Cardiovascular Disease

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by

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Abstract

The purpose of the presented research and systematic review is to determine the associated impact resting heart rate has on development of cardiovascular disease. A literature review was conducted through electronic databases: PubMed, Clinical Key and Dynamed Plus. No limitation of timeframe was used when researching as few studies are available correlating resting heart rate and its associated development of cardiovascular disease. Research points to limitations of lowering resting heart rate due to adverse effects on blood pressure. Additionally, tachycardia is addressed through several methods including lifestyle modification and pharmacologic therapy. Comorbidities such as obesity, low *body mass index* (BMI), diabetes, hypertension and preexisting heart disease are influential factors in target heart rate therapy. Research concludes individuals benefit from a reduction in resting heart rate to less than 80 beats per minute, regardless of gender or ethnicity. Reduction of heart rate below 60 beats per minute shows no added benefit and can cause a paradoxical rise in blood pressure as a compensatory mechanism by the cardiovascular system, ultimately negating the benefits of lowered resting heart rate.

Keywords: resting heart rate, resting tachycardia, resting bradycardia, atherosclerosis, cardiovascular disease, morbidity, and mortality.

Introduction

According to the American Heart Association (2016), heart failure affects approximately 5.7 million adults in the United States, with the number of heart failure diagnosis increasing each year. The purpose of this study is to compare the range of *beats per minute* (bpm) of the heart and the effects resting bradycardia (slow heart rate <60 bpm) and resting tachycardia (fast hear rate >100 bpm) to target heart rate range (60-100 bpm). These comparisons will investigate if those with bradycardia are at an increased risk for cardiovascular disease, morbidity and mortality, and if a reduction in resting tachycardia provides a proven reduction in cardiovascular disease, morbidity and mortality. This focused study will consider varying methods of heart rate reduction in those suffering from resting tachycardia such as a modified lifestyle habits or medication supplement such as beta blockers.

Statement of the Problem

In the United States, heart disease is the leading cause of death in men and women of most ethnicities, accounting for approximately 610,000 deaths annually according to the CDC (2019). With guidelines aiming to reduce blood pressure and reduce *atherosclerosis* (plaque deposits in the blood vessels), how closely is heart rate, especially resting tachycardia, being looked at in the development of heart disease, associated morbidity and mortality? All major contributing factors of cardiovascular disease need to be addressed if heart disease, associated morbidity and mortality are to be significantly reduced, this includes bradycardia, resting tachycardia and their effect on cardiovascular disease.

Research Questions

In the general population, does variation in heart rate reduce chance of cardiovascular disease, morbidity and mortality in those with bradycardia?

Does tachycardia increase the risk for cardiovascular disease, morbidity and mortality, compared to those with a heart rate in target range?

Research Methods

A literature review of meta-analysis, randomized control trials (RCTs), and systematic reviews were conducted through electronic databases: PubMed, Clinical Key and Dynamed Plus. To define a set literature review, mesh terms and keyword terms were used which discussed resting heart rate and its correlation with morbidity and mortality. Mesh terms used include *resting heart rate, resting tachycardia, resting bradycardia, atherosclerosis, cardiovascular disease, morbidity, and mortality*. Publication time frames were not included due to limitation of published information regarding the research topic. Additionally, peer reviewed medical journals were utilized for topic research which include The Journal of the American Medical Association (JAMA), and The Journal of the American College of Cardiology (ACC). Meta-analysis, systematic reviews, randomized control trials (RCTs) were included, providing adequate data for the proposed research topic.

Literature Review

Review of literature shows numerous studies focusing on the correlation between bradycardia or tachycardia and an association of developing cardiovascular disease, reduction in cardiovascular events, or reduced morbidity and mortality. The study of lifestyle modification and medication therapy are considered for optimal reduction of cardiovascular events in those with varying resting heart rate.

Theme 1: Bradycardia and its Associated Risk of Cardiovascular Disease and Mortality.

Bradycardia is defined as a resting heart rate that is slower than expected, generally at a pace of <60 bpm. An abundance of factors can contribute to a slower heart rate, including increased age, high levels of physical fitness, genetics and family history. As the heart beats slower, the body responds with physiologic changes such as increased arterial pressure. This reaction from the body helps maintain adequate perfusion of tissue with blood due to decreased heart rate. The goal of the study by Messerli et al. (2016) was to review physiological and pharmacological bradycardia and its effect on development of all-cause mortality in those with and without comorbidities.

The methods conducted in 2016 include meta-analysis of 22 randomized controlled studies involving 60,000 patients, reference to peer-reviewed clinical trials studied in the Journal of the American Medical Association (JAMA) Internal Medicine, the Journal of the American College of Cardiology (ACC), and reference to primate studies on the effects of atherogenic diet.

Results of the study concluded an increase in resting heart rate is highly linked to the development of adverse cardiovascular conditions and outcomes. In those with heart failure, the use of negative chronotropic drugs (beta blocker, calcium channel blocker) reduced cardiovascular events and exacerbations. In patients with hypertension, reduction of resting

heart rate increases the chance of cardiovascular event, through increased central systolic blood pressure and decreased brachial blood pressure, causing a ventricular – vascular mismatch. A lowering of resting heart rate is shown to cause an increase in central systolic blood pressure, which overrides the potential benefit when done in those with coronary artery disease.

A limitation of this study is not knowing the effects on cardiac function and its increased longevity. No data was given to inform the reader of those suffering from heart failure and whether an increase in ejection fraction was found through reduction of resting heart rate.

The goal of the study by Dharod et al. (2016) was to complete a Multi-Ethnic Study of Atherosclerosis (MESA), studying asymptomatic bradycardia and its incidence on cardiovascular disease and mortality.

The method used in this study was the retrospective analysis of 6733 men and women of multiple ethnicities from the years 2000 – 2002. These patients were followed for 10 years post-study for observation of adverse cardiovascular outcome. The analysis was performed and completed in 2014.

The results of the study found of the 6733 participants, an average resting heart rate of 63 bpm, with an SD of 9.5, was obtained. Heart rate and the corresponding population was divided into multiple categories: <50 bpm (11.2%), 50-59 BPM (39.1%), 60-69 bpm (33.9%), 70-79 bpm (11.5%), and 80 or greater bpm (4.2%). The patient population on heart rate modifying medication and their corresponding heart rate are as follows: the mean (SD) heart rate was 60 (9.7) bpm, heart rate less than 50 bpm (11.2%), heart rate of 50 to 59 bpm (39.1%), heart rate of 60 to 69 bpm (33.9%), heart rate of 70-79 bpm (11.5%); heart rate of 80 bpm or greater (4.2%). Of the most common heart rate modifying medications, 93% were on a beta-blocker, with the remaining 7% being on digoxin or an antiarrhythmic drug.

Patients with a resting heart rate of <60 bpm and not on heart rate modifying medications had similarities including lower BMI, less likely to have diabetes, increased physical activity and of male sex. In addition, these individuals were more likely to have changes represented on an electrocardiogram (EKG), which is a real-time tracing of the hearts rate, rhythm, and electrical pathways detected through specifically placed leads. Patients who were on a heart rate modifying medication and have a resting heart rate of <60 bpm or >80 bpm showed an increased risk of mortality due to cardiovascular disease, compared to those who are not on heart rate modifying medication. Below is a table showing the increased hazard ratio in patients on heart rate modifying medications and those who are not on heart rate modifying medications.

Table 4. Hazard Ratios for Incident Cardiovascular Disease (CVD) and Mortality by Heart Rate (HR) Category[a]

HR Category, beats per minute	Model 1		Model 2		Model 3		Model 4	
	Hazard Ratio (95% CI)	*P* Value for Trend	Hazard Ratio (95% CI)	*P* Value for Trend	Hazard Ratio (95% CI)	*P* Value for Trend	Hazard Ratio (95% CI)	*P* Value for Trend
Incident CVD								
Participants not taking HR-modifying drugs								
<50	1.10 (0.73-1.67)		1.03 (0.68-1.57)		1.02 (0.67-1.55)		1.07 (0.71-1.63)	
50-59	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
60-69	1.26 (1.00-1.59)	<.001	1.17 (0.93-1.48)	.13	1.17 (0.93-1.48)	.14	1.19 (0.94-1.51)	.16
70-79	1.41 (1.08-1.84)		1.26 (0.96-1.66)		1.26 (0.96-1.65)		1.27 (0.96-1.67)	
≥80	2.05 (1.46-2.89)		1.59 (1.11-2.27)		1.57 (1.10-2.24)		1.55 (1.08-2.22)	
Participants taking HR-modifying drugs								
<50	1.32 (0.71-2.47)		1.28 (0.68-2.40)		1.28 (0.68-2.39)		1.27 (0.68-2.37)	
50-59	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
60-69	1.88 (1.22-2.87)	.04	1.88 (1.22-2.90)	.06	1.89 (1.22-2.92)	.06	1.84 (1.19-2.86)	.10
70-79	1.58 (0.87-2.86)		1.58 (0.86-2.92)		1.59 (0.86-2.92)		1.58 (0.85-2.92)	
≥80	2.27 (0.99-5.22)		2.17 (0.91-5.14)		2.20 (0.92-5.22)		1.80 (0.75-4.29)	
Mortality								
Participants not taking HR-modifying drugs								
<50	0.71 (0.47-1.09)		0.74 (0.49-1.13)		0.72 (0.47-1.10)		0.71 (0.41-1.09)	
50-59	0.82 (0.66-1.02)		0.85 (0.69-1.07)		0.85 (0.68-1.06)		0.83 (0.67-1.04)	
60-69	1 [Reference]	<.001	1 [Reference]	.002	1 [Reference]	.002	1 [Reference]	.002
70-79	1.21 (0.97-1.52)		1.21 (0.97-1.53)		1.22 (0.97-1.53)		1.21 (0.96-1.52)	
≥80	1.58 (1.16-2.15)		1.51 (1.10-2.07)		1.52 (1.11-2.08)		1.49 (1.08-2.05)	
Participants taking HR-modifying drugs								
<50	2.39 (1.41-4.06)		2.36 (1.36-4.09)		2.43 (1.39-4.22)		2.42 (1.39-4.20)	
50-59	1.54 (0.99-2.40)		1.60 (1.02-2.52)		1.62 (1.03-2.54)		1.65 (1.05-2.59)	
60-69	1 [Reference]	.001	1 [Reference]	.001	1 [Reference]	.001	1 [Reference]	.002
70-79	1.39 (0.75-2.56)		1.36 (0.74-2.52)		1.36 (0.74-2.52)		1.35 (0.73-2.50)	
≥80	4.38 (2.14-8.94)		3.91 (1.83-8.32)		3.87 (1.82-8.25)		3.55 (1.65-7.65)	

Abbreviation: HR, heart rate.

[a] Model 1 adjusts for age, sex, race, education, alcohol use, smoking, and any vigorous activity. Model 2: model 1 plus diabetes mellitus, total cholesterol level, high-density lipoprotein cholesterol level, lipid-lowering drug use, body mass index, creatinine level, systolic blood pressure, and diastolic blood pressure, Model 3: model 2 plus hypertension drugs. Model 4: model 3 plus coronary artery calcium prevalence and major electrocardiographic abnormalities.

Dharod, A., Soliman, E., Dawood, F., Chen, H., Shea, S., Nazarian, S., & Bertoni, A. (2016). Association of asymptomatic bradycardia with incident cardiovascular disease and mortality. *Journal of American Medical Association Internal Medicine*, *176*(2), 219. http://dx.doi.org/10.1001/jamainternmed.2015.7655

A limitation of the study is the underlying reason a patient was taking a heart rate modifying medication at the beginning of the study. Reasons for taking such medications, such as arrhythmia or heart failure were not reported to the MESA trial. (Dharod et al. 2016)

The goal of the study by Makita et al. (2014) was to compare the effects of bradycardia and the development of cardiovascular disease to the well-established findings of tachycardia and its known comorbidity of cardiovascular disease events in men.

The method used in this study, according to Makita et al. (2014) was a controlled study involving 17,766 patients, 5,958 of which were men. The study excluded men or women with existing atrial fibrillation, those with history of cardiovascular disease, and those on anti-hypertensive therapy. Patients between the ages of 40-79 were divided into four groups based on their resting heart rate/ resting pulse rate. These heart rate groups were; <60 beats per minute, 60-69.5 beats per minute, 70-79.5 beats per minute, and those equal or >80 beats per minute. The end of the study was set when a patient suffered from myocardial infarction, stroke, or sudden death.

The results of the study were based on a mean follow-up time frame of 5.6 years. Noted cardiovascular events occurred 213 times in men and occurred 186 times in women. Of the groups based on resting heart rate, increased risk of cardiovascular disease events was greatest in men with a resting heart rate of <60 beats per minute, as well as the group of men and women whose resting heart rate was equal to or >80 beats per minute. These groups and their associated risk were compared with the reference group with a resting heart rate of 60–69.5 beats per minute, (hazard ratio [HR] = 1.73, $p = 0.005$ and HR = 2.01, $p < 0.001$) for bradycardia and tachycardia respectively. (Makita et al. 2014).

A limitation of the study is the population of men versus women who were involved in the study. Of the 17,766 participants, 5,958 of the individuals were male. This is a female to male participant ratio of nearly 2:1.

Theme 2: Target heart range and its Associated Cardiovascular Risk.

Target heart range is defined as a resting heart rate between 60 bpm and 100 bpm according to the Mayo Clinic (2019). At this range, the body's optimal perfusion of blood to vital organs is sufficient, without adverse effects of increased blood pressure, causing vascular damage to small vessels. The goal of the study by Steward et al. (2017) is to assess prevention guidelines and their efficacy in established countries such as the United Kingdom and the United States, as well as developing countries who change their lifestyle habits throughout time.

Methods used in this study include review of cardiology guidelines for cardiovascular disease prevention published by the National Institute for Health and Care Excellence (NICE) guidelines, European Society of Cardiology (ESC) guidelines, as well as guidelines from the American Heart Association (AHA) and American College of Cardiologists (ACC). (Stewart et al. 2017)

The results from the study focused on lifestyle and their modification according to the guideline references noted in the methods portion. Lifestyle modifiers focused on areas including; exercise, diet, alcohol consumption, weight, smoking cessation. Additional modifiers considered that involve medical therapy include; anti-hypertensive therapy, lipid lowering therapy, anti-platelet therapy and blood glucose control.

In addressing lifestyle activity, populations are encouraged to perform exercise of moderate intensity for 150 minutes per week or 75 minutes of vigorous exercise per week (AHA, NICE, ESC).

Populations are recommended to reduce saturated fat and sugar intake with an increase in vegetable and fruit intake of up to five portions a day (AHA, NICE).

The limiting of alcohol consumption is a topic of discussion among many health professionals and entities. In general, light alcohol consumption is seen to have anti-platelet effects, reducing the risk of abnormal clotting, while moderate to heavy drinking shows proven risk for cardiovascular disease incidence (ESC, NICE). European data indicate that smoking doubles the 10-year CVD mortality rate whilst 30% of US CVD mortality is attributable to smoking. Eckel et al. AHA/ ACC (2013). According to Piepoli et al. (2016), and the European guidelines for cardiovascular disease prevention in clinical practice advise the practice of stopping smoking is the single most cost-effective intervention in CVD prevention, and some benefits are seen within months of cessation.

In patients of varying BMI, those with a BMI >25 show risk of developing cardiovascular disease, with an optimal BMI of 20-25. In contrast, BMI of <20 shows a rise in all cause mortality, and this range is generally not recommended.

Lipid lowering therapy is a common practice in primary care. Of total cholesterol, low density lipoprotein concentration (LDL-C) is the value with the most correlation regarding the development of cardiovascular disease. The lowering of LDL-C by 1.0 mmol/L corresponds to a 20-25% reduction in cardiovascular disease mortality or non-fatal MI. (Piepoli et al. 2016).

Anti-hypertensive therapy is an independent risk factor. According to Steward et al. (2017), as a general consensus through a collaborative prospective studies meta-analysis of 61 studies, those who have a blood pressure >115/75, where each 20mmHg rise in systolic blood pressure (115) or a 10mmHg rise in diastolic blood pressure (75) doubles an individual's risk for cardiovascular disease event occurrence.

Blood glucose control has largely been a contributing factor to preventing the development of diabetes mellitus and its associated comorbid effects on cardiovascular disease. In those with diabetes mellitus, sodium/glucose transporter 2 inhibitor class of oral hypoglycemics such as empagliflozin have been shown to significantly reduce all-cause mortality by 32%, as well as CVD death by 28% and HF by 35% in comparison with standard care. (Zinman et al. New England Journal of Medicine 2015)

Anti-platelet therapy is viewed as a secondary therapy option in those with diabetes mellitus and in those with a cardiovascular disease risk of equal to or >10% (American College of Chest Physicians, ECC) as in those without monotherapy, the bleeding risk is greater than cardiovascular disease complication

This study is lacking guidelines set forth by non-westernized cultures. The United Kingdom and the United States are countries of diversity, although are already established countries. Influence of guidelines in developing countries would be a large benefit to efficacy in settings of lower cardiovascular disease prevalence.

This study focuses on populations that are within target heart range and addresses risk factors and modifiable lifestyles that contribute to the development and exacerbation of cardiovascular disease. For established countries, prevention and modification of established lifestyles are key aspects to addressing active cardiovascular disease and those at high predisposition that can be addressed through modifiable factors.

The goal of the study by Kubota et al. (2017) was to follow individuals of varying heart rate and assess the incidence and risk of lifetime cardiovascular disease development.

The method used in this study was to study a population consisting of 9,744 participants, who were free of cardiovascular disease at the time of study. An estimation using a lifetable was used to calculate risk among the participants, who ranged in age of 45-85. Cardiovascular disease, categorized as coronary heart disease, heart failure, and stroke was calculated through heart rate variables including a standard deviation measurement of the resting heart rate of involved individuals [SD_{NN}]. Additionally, the root mean square of successive differences of successive resting rate intervals, the mean of all normal resting rate intervals [$mean_{NN}$], low-frequency [LF] and high-frequency [HF] power, and the LF/HF ratio) (Yasuhiko et al. 2017)

The results using the life-table estimation calculated 192,110 person years, in which 2,856 cardiovascular events occurred over the 9,744 involved participants. According to Kubota et al. "Cox regression analyses with the false discovery rate method correction showed independent associations of SD_{NN}, $mean_{NN}$, LF, and LF/HF in women with CVD. Lifetime CVD risks in the lowest compared with the highest tertile were significantly increased in men for LF/HF (51.3% [95% confidence interval, 47.3–54.7] vs. 43.9% [40.1–47.2]), and in women for SD_{NN} (39.4% [36.0–43.0] vs. 29.9% [26.3–33.0]), $mean_{NN}$ (39.3% [35.7–42.7] vs. 28.9% [25.7–31.7]), LF (39.4% [35.9–43.0] vs. 30.0% [26.2–33.2]), and LF/HF (37.6% [33.9–40.9] vs. 30.0% [26.8–32.7])" (Kubota et al. 2017, p. 619). A modest association of lower life-time cardiovascular disease risk is seen in those that have greater heart rate variability.

The use of a prediction lifetable, which is a cohort table used to predict the cause of mortality in a specific population over ones entire lifetime, is not a desirable application due to its limitations which may impact results based on real world variation as opposed to a predictive value. The table does not account for personal variation in diet, lifestyle or development of comorbidities.

This study accounts for those whose heart rates are within target range but vary through one's life and the predicted life-long effect that has on development of cardiovascular disease.

The goal of the study performed by Maclehose et al. (2016) is to show the association between low heart rate variability and the increased incidence of all-cause cardiovascular mortality.

Methods used involve a study referred to as The Atherosclerosis Risk in Communities (ARIC) study, which measured a patient's heart rate variability by using two-minute EKG readings in 12,550 participants, who were middle-aged at baseline of the study between years 1987–1989. According to Fyfe-Johnson (2016), the heart rate variability indices were calculated using the standard deviation of the resting heart rate intervals (SD_{NN}), the mean of all normal resting heart rate intervals ($mean_{NN}$), the root mean square of successive differences of successive resting heart rate intervals (RMSSD), low (LF) and high (HF) frequency power, and the LF/HF ratio. Heart rate variability measurements were categorized into five groups. Incident stroke was adjudicated through 2011. Cox regression was used to estimate hazard ratios (HRs) with the lowest heart rate variability group as the reference group, with and without classification by diabetes mellitus prevalence.

The result of the study shows that at visit one (baseline), of the 12,550 participants, 6.5% suffered from a stroke, which correlated with a lower heart rate variability. In the groups of those with lower heart rate variability, the population was found to contain a higher proportion of women, those with increased levels of stress, those with higher heart rate and those with hypertension and taking anti-hypertensive medication. Cox regression analysis showed a correlation between those with low heart rate variability and incidence of stroke. A separate consistent factor was the increased incidence in stroke and those who have diabetes mellitus.

According to Fyfe-Johnson et al. “Stratified analyses restricted to people with diabetes mellitus consistently showed higher stroke risk associated with the lowest HRV quintiles for SD_{NN} (HR, 2.0; 95% confidence interval [CI], 1.1–4.0), root mean square of successive differences in RR intervals (HR, 1.7; 95% CI, 0.9–3.2), low frequency power ratio (HR, 1.5; 95% CI, 0.8–3.0), and high frequency power (HR, 1.7; 95% CI, 0.9–3.0).” (Fyfe-Johnson et al. 2016, p. 1455). Despite traditional cardiovascular disease risks, incidence of stroke is found to be higher in individuals with diabetes mellitus.

A limitation of the study is the unknown cause of cardiovascular disease, cardiovascular dysfunction or cause of stroke in those with diabetes. Predisposing secondary factors may be of unknown influence.

Theme 3: Tachycardia and its Associated Risk of Cardiovascular Disease.

The goal of the study by Perret-Guillaume et al. (2009) is to review the correlation between heart rate and the development of cardiovascular disease. Additionally, drug classes will be discussed that have potential benefit in clinical conditions which may have increased heart rate as a comorbidity.

The methods used in this study include focus on the general population, the elderly, those with hypertension and those who are status post-myocardial infarction.

The results of the study agree with many solidified studies correlating tachycardia with increased incidence of atherosclerotic lesions within the cardiovascular system. Palatini (1999) notes a study conducted on Army officers correlating a two to three times higher frequency of developing hypertension in those with transient tachycardia, as compared to those who had heart rate within target, dating back to 1945. Levy, White, Stroud (1945) were the first to publish in the Journal of American Medical Association a found correlation between resting tachycardia

and increase in cardiovascular mortality. Since then, subsequent studies with supportive evidence have been published backing the strong link between tachycardia, associated cardiovascular disease, noting resting heart rate as a strong indicator of mortality from cardiovascular causes.

In the elderly, Sutton-Tyrrell, Alcorn, Herzog, et al studied 187 patients with systolic hypertension. In the studied patients, a correlation between those with a resting heart rate and development of carotid stenosis was evident (p=0.013). Moreover, according to Perret-Guillame et al. (2009) " Two recent observational studies conducted in elderly people found a clear relationship between the level of HR and the rate of cardiovascular mortality.[15,16] In the CASTEL study[15] the predictive power of HR for mortality was investigated in 763 men and 1175 women aged 65 years or older stratified by quintiles of HR. After adjustment for other risk factors, relative risk for cardiovascular mortality was 1.38 for the men with HR >80 beats/min (top quintile) compared with those of the three intermediate quintiles, and 0.82 for the men with HR.".

In patients with hypertension, cardiovascular relative risk was adjusted for those who smoke, factored in total cholesterol, and those with left ventricular hypertrophy. With previous mentioned risk factors considered, incidence for cardiovascular mortality was 1.68 in males and 1.70 in females. For sudden death the adjusted odds ratios were 1.93 and 1.37, respectively, in the men and women with hypertension. (Palatini, 1999).

Pathogenetic mechanisms of tachycardia and cardiovascular disease include coronary attack, increased sympathetic tone leading to increased left ventricular size, coronary thrombosis through increased blood viscosity, a procoagulant state, and platelet activation. The correlation between tachycardia and atherosclerosis lies in arterial wall stress and atherosclerotic deposits.

As resting heart rate remains at a state of chronic tachycardia, arterial wall stress increases. The state of increased arterial wall stress and pressure causes higher incidence of atherosclerotic deposits. These plaque deposits cause an inflammatory response on arterial walls, leading to atherosclerotic lesions. As plaques and lesions increase in number and size, the incidence for cardiovascular events, myocardial infarction or stroke, markedly increases. Increased sympathetic tone leading to left ventricular hypertrophy creates a cardiovascular environment where cardiac muscle does not receive the amount of oxygen required to sustain the enlarged ventricle muscle, causing ischemia and leading to myocardial infarct. Increased blood viscosity and platelet activation creates increased probability of myocardial infarction and stroke through ischemia secondary to a lodged thrombosis. Palatini (1999).

In post-myocardial infarction patients, the heart rate is often correlated to the diminished performance of the left ventricle. According to Palatini (1999), clinical experiments show tachycardia in those who suffered from acute myocardial infarction contributed to reduced left ventricular performance. In patients with restricted coronary blood flow, tachycardia further induces cardiac ischemia which precipitates the event of infarct and possible arrhythmia.

Beta blockers are a medication type that blocks beta-1 receptors in the heart from the hormone epinephrine, reducing rate and force of contractility, ultimately reducing heart rate and blood pressure. A meta-analysis of 29 trials in which patients were assigned to early treatment with β-blockers revealed a 13% reduction in overall mortality ($p = 0.02$). (Teo, Yusuf, Furberg, 1993). Clear benefit of beta-blocker administration was seen in those whose heart rate decreased by 14 beats per minute. In those whose heart rate didn't decrease by at least eight beats per minute, no benefit of beta-blocker administration was observed. (Kjekshus 1986). Calcium antagonists are another favorable option for lowering resting heart rate and blood pressure

through peripheral arterial action. In addition to relaxing the arterial wall tension in peripheral blood flow, calcium channel blocking agonist verapamil was observed to easily cross the blood brain barrier, being detectable in the cerebral spinal fluid. This may have secondary benefit by decreasing sympathetic tone, which also reduces resting heart rate. At the time of this study, centrally acting drugs such as clonidine or guanfacine seemed appropriate for reducing resting heart rate but were not favored due to side effects of dry mouth, sedation and impotence. (Perret-Guillaume et al. 2009)

The limitation of this study is the advancement of heart rate drug development at the time of the study. New methods and advancements in heart rate control, such as the class hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers which more effectively reduce heart rate in those with normal sinus rhythm while allowing adequate perfusion to tissue.

The goal of the study conducted by Shabtaie et al. (2019) is to establish epidemiologic data in patients suffering from inappropriate supraventricular tachycardia (IST). This includes onset of symptoms, co-morbidities and the long-term outcome from the effects of IST.

A retrospective review of all patients diagnosed with IST was performed at the Mayo Clinic (Rochester, MN) from 1998-2018. Demographic data and clinical outcomes of the patients with IST were compared to an age and gender matching control group which had atrioventricular nodal reentry tachycardia (AVNRT).

In the twenty-year study period, 305 patients were identified. According to Shabtaie et al. 2019, the mean follow-up was 3.5 years, with 92.1% female and mean age 33.2 ± 11.2 years. In this study group, the most frequent circumstantial condition triggering IST was pregnancy (7.9%), followed by infectious illness (5.9%). The most common comorbid conditions were

depression (25.6%) and anxiety (24.6%). Left ejection fraction was measured in patients at time of diagnosis, with a mean of 62.3 ± 6.2%. At a follow-up timeframe with a mean 4.9 ± 4.3 years (baseline LVEF 59.8 ± 10.7% vs. subsequent 61.4 ± 8.1%, p = 0.2971). (Shabtaie et al. 2019). In the twenty-year study period, two deaths occurred, one of which was cardiac related as a result of myocardial infarction. A comparison between the IST and AVNRT groups show no correlation of excess mortality.

A limitation of the study is any significant events occurring in those with Inappropriate Supraventricular Tachycardia prior to diagnosis, and the beginning of the study.

The goal of the study performed by Williams et al. (2009) is to evaluate heart rate as an independent risk factor for the development of cardiovascular disease.

The method used in this study includes heart rate measurement in 1,407 men and 1,134 women age 65-70 without history of major cardiovascular disease at the time of the study. Data collected was used to predict morbidity and mortality along with predicted probability on minimum age of survival.

The results of the study look at several factors influencing the association between heart rate and development of cardiovascular disease:

Mechanism between heart rate and cardiovascular complications: According to Perret-Guillaume, Joly and Benetos 2009, Tachycardia may be due to imbalance of autonomic nervous system tone. This autonomic nervous system imbalance results in increased cardiovascular events and tachycardia due to increased myocardial oxygen consumption, decreased blood perfusion into tissues, induced cardiac muscle fatigue and elastic fiber fracture in the arterial walls.

“A clinically significant increase in the cardiovascular risk has been observed in subjects with a heart rate more than 80 bpm. Data obtained in subjects with coronary disease showed that those with even moderately accelerated heart rate (>70 bpm) experience benefits when heart rate was pharmacologically reduced with bradycardic drugs.” (Perret-Guillaume et al. 2009, p.7).

Several studies correlating blood pressure and heart rate were conducted by Gillum, Makuc and Feldman 1991 (Pulse rate, coronary disease, and death), by Benetos, Rudnichi, and Thomas 1999 (Influence of heart rate on mortality in a French population), and by Morcet, Safar, and Thomas 1991 (Associations between heart rate and other risk factors in a large French population). These studies found those with untreated hypertensive states, on average had a heart rate that was six beats per minute faster than individuals who were normotensive. This correlation was found in a variety of patients, regardless of age, sex or body mass index.

Perret-Guillaume et al. 2009 discuss the association between elevated heart rate, sympathetic activity, and metabolic syndrome. The correlation between the three suggests that metabolic disturbances, such as insulin resistance, hyperglycemia, and hyperlipidemia, which increase sympathetic tone. Over time the increase in sympathetic tone causes sustained tachycardia which results in chronic blood pressure elevation. Sustained hypertension is strongly correlated with cardiovascular disease.

According to the European Society of Cardiology and the European Society of Hypertension, these guidelines set forth in 2007 first recognized heart rate as an independent risk factor for increased all cause mortality and targets were set for pharmacologic therapy, especially in high-risk populations.

The limitation to this study is missing data from high risk populations including those with heart failure, long standing hyperlipidemia, and diabetes. Comparative measures against a

high-risk population and a low risk population would signify the impact heart rate has on those with comorbidity.

Discussion

When comparing the risk of cardiovascular disease development, exacerbation of comorbidities (coronary artery disease, diabetes) and reduced overall mortality, resting heart rate variation shows key benefits and risk factors.

In those with resting bradycardia (<60 bpm), benefits are seen in select populations. The population that benefit the most are those with a resting heart rate of 60 bpm or less, who are not on heart rate modifying medication. In this population, a reduction in cardiovascular disease events (MI, acute coronary syndrome, development of coronary artery disease, cardiovascular changes on an electrocardiogram) is seen. Individuals with a heart rate of <50 had similarities, regardless of ethnicity. These individuals were mostly male gender, had a lower BMI, were more physically active compared to the rest of the study group, and were less likely to have diabetes. When a population is on a heart rate modifying medication such as beta-blockers or calcium-channel blockers, mortality and exacerbation of comorbidities is seen, especially if heart rate is <50 bpm. As heart rate is reduced through heart rate modifying medication an increase in systolic blood pressure is observed. This rebound in systolic blood pressure negates the benefit of reducing an individual's resting heart rate.

While individuals with bradycardia who are not on heart rate modifying medications are at reduced risk of cardiovascular events when compared to those with a resting heart rate of >80 bpm, they are still at an increased risk compared to individuals with a heart rate between 60 – 80 bpm. Patients whose heart rate is within target range are observed for other cardiovascular risk factors such as; smoking, poor diet, lack of exercise, alcohol consumption and poor glucose control. The modifiable risk factor with the biggest impact on cardiovascular health at time of cessation is smoking. Smoking accelerates the deposit of plaque within arteries and remodels

vascular pathways within the body, increasing the risk for cardiovascular disease and stroke. Additionally, reduction of saturated fat intake, alcohol consumption and control of blood glucose play a large role in reduction in the development of atherosclerosis and cardiovascular disease. With reduction of saturated fat intake, the reduction of LDL-C is regarded as the largest offending lipoprotein, contributing to fat deposition within tissues and blood vessels. With blood glucose control comes the prevention or control of diabetes. According to the American Diabetes Association (2020) a non-diabetic individual's fasting blood glucose levels should be less than 100 mg/dL to prevent the risk of being in a prediabetic state. Individuals with a fasting blood glucose of 100 – 125 mg/dL are considered at high risk for development of diabetes. Diabetes is diagnosed with two fasting blood glucose levels of 126 mg/dL or higher in an asymptomatic individual. Additionally, a glucose tolerance test can be performed in clinic with a blood glucose level measured 2 hours after consumption of a glucose drink administered by your healthcare provider. Lastly, a test called a hemoglobin A1C measures the 3-month average of blood glucose in your body. A reading of 6.5% or higher is indicative of diabetes. A diagnosis of diabetes puts an individual at higher risk for cardiovascular disease and stroke. In diagnosed diabetics, an A1C of 7% or less is viewed as optimal control for reducing the risk of developing cardiovascular disease or stroke. These lifestyle choices are most seen as risk factors in developed countries and westernized cultures, where such products and common diet practices are observed. For individuals whose heart rate is between 60 – 80 bpm, prevention of cardiovascular disease development is the key tactic to ensuring reduced all cause mortality with cardiac involvement.

Those who suffer from resting tachycardia (>80 bpm) are the population who are at the highest risk for development of cardiovascular disease and associated mortality. Resting

tachycardia is the heart rate category with the highest risk of mortality due to cardiovascular involvement. Factors that contribute to this increased mortality include increased blood pressure which contributes to increased heart size due to opposing systemic back pressure, causing an enlargement of the left ventricle which leads to heart weakness and failure. Additionally, hypertension secondary to tachycardia increases platelet activation and atherosclerotic deposits within arteries. Platelet activation and atherosclerotic plaque cause a *hypercoagulable state* (increased likelihood of platelets sticking to walls of arteries which induces the formation of a clot), which increase an individual's chance for development of MI, acute coronary syndrome due to poor heart perfusion, and stroke. Medication to reduce heart rate such as beta-blockers or calcium-channel blockers help reduce cardiovascular events. Additionally, calcium-channel blockers reduce blood pressure, providing reduced mortality from secondary coronary events. In individuals with comorbidities such as diabetes or hyperlipidemia, additional medication to reduce total cholesterol will help lower the risk of coronary artery disease or stroke due to the development of atherosclerosis.

Application to Medical Practice

The information provided in the literature review allows medical providers to take the benefits shown in reducing resting tachycardia in the patient population and apply it to cardiovascular disease prevention and apply it to those with subsequent morbidities to reduce overall mortality. Information provided in the literature review also shows the limitation of heart rate reduction and its limited benefits in certain patient populations, such as those already in target range heart rate, and those whose heart rate and correlating blood pressure are optimized for their current health status.

Conclusion

Through reduction of resting heart rate, the risk of developing cardiovascular disease is reduced in men and women of most races and ethnicities. Studies of bradycardia and associated cardiovascular disease and mortality show those individuals who have a heart rate less than 60 beats per minute were not associated with increased cardiovascular disease or mortality, whether they were on heart rate modifying drugs or not. Patients with a resting target heart rate between 60 and 80 have no increased association with cardiovascular disease and mortality, independent of other comorbidities

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