Send Orders for Reprints to reprints@benthamscience.net

Current Cardiology Reviews, 2021, *17*, e160721189770

REVIEW ARTICLE

Analysis of Heart Rate Variability and Implication of Different Factors on Heart Rate Variability

Reena Tiwari[1], Ravindra Kumar[2], Sujata Malik[3], Tilak Raj[4] and Punit Kumar[5,*]

[1]Department of Morphology and Physiology, Karaganda Medical University, Karaganda 100008, Kazakhstan; [2]Department of Pathology, Karaganda Medical University, Karaganda 100008, Kazakhstan; [3]Department of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, Kalyanpur, Kanpur, Uttar Pradesh-208016, India; [4]Department of Zoology, Pt. Neki Ram Sharma Government College, Rohtak, Haryana 124001 India; [5]Department of Biomedicine, Karaganda Medical University, Karaganda 100008, Kazakhstan

Abstract: ***Background*:** The heart is the central organ of the circulatory system, which maintains the flow of blood along with the transport of nutrients to different cells and tissues. A well-functioning cardiac state is a complicated mode of changeability. A healthy heart is not only about oscillation, as the rhythmometer is not the same in every circumstance. Heart rate shows variations so that it can be regulated according to psychophysiological conditions to maintain the effect of the internal-external stimulus.

***Objective*:** The main objective of this review is to provide a piece of all-inclusive information about heart rate variability (HRV) and different variables affecting HRV. The direct interconnection so that HRV can be used in clinical practices.

***Methods*:** This review article contains a detailed survey of literature about HRV available in different online sources such as; Google Scholar, Science Direct, PubMed, and Web of Science, *etc.* In this review, the authors have focused on the role of the autonomic nervous system in the regulation of HRV and the role of various factors affecting HRV.

***Results*:** The variation in the time between two heartbeats is termed as HRV. It is one of the indicators of many pathological conditions related to cardiovascular health. It provided reliable information about the interaction of the sympathetic and parasympathetic nervous systems. The analysis of the variation of heart rate is a well-known non-invasive technique to identify the functioning of the autonomic nervous system. The autonomic nervous system (ANS) depends on the sympathetic and parasympathetic nervous system for transferring information. The cardio-accelerating center, lungs, and non-striated muscles are innervated by cardiac sympathetic nerves. This division of ANS latches upon the heart accordingly *via* the cervicothoracic ganglion and vagus nerve. It is found that cardiac normal variability depends upon this stimulation towards the sinoatrial node (pacemaker), which can be evaluated by analyzing the HRV. In human-based studies, it has been found that a low level of HRV is one of the main causes of death rate among adults. Hence, HRV helps in identifying the risk of cardiac diseases and the state of ANS.

***Conclusion*:** The heart plays a vital role in the human body and the well-functioning of the cardiac system is the need for a healthy life. The heart contains its nervous system termed as neurocardio system in which ANS plays a key role in which the sympathetic and parasympathetic systems interplay to regulate HRV. High HRV is associated with healthy condition, while low HRV is associated with pathological conditions. The HRV is influenced by various variables such as; pathological, physiological, psychological, environmental factors, lifestyle factors, and genetic factors, *etc.*

ARTICLE HISTORY

Received: June 16, 2020
Revised: October 10, 2020
Accepted: October 20, 2020

DOI:
10.2174/1573403X16999201231203854

Keywords: Heart, heart rate variability, autonomic nervous system, brain-heart connection, cardiac ganglia, sympathetic nervous systems, parasympathetic nervous systems.

* Address correspondence to this author at the Department of Clinical Immunology, Allergology and Microbiology, Karaganda Medical University, Karaganda 100008, Kazakhstan; E-mail: punitdariyapur@gmail.com

1. INTRODUCTION

The heart is considered an exclusive structure that plays a vital role in the human body. Now, it is well known that the heart is an electromechanical pump that propels oxygenated blood proportionately to the demand and receives deoxygenated blood from all over the body [1], and this activity depends upon the myocardiocytes of the myocardium (Frank-Starling Law). Though it is not clear that stress or other determinants may alter the cardiac structure and functioning but similar to other human organs, the heart is also prone to diseases such as hypertension, heart stroke, cardiac myopathies, angina, valvular diseases, *etc.* Its functioning is also influenced by age, lifestyle, lack of exercise, physical activity, metabolic disorders, nutrition state, physiological changes, and pathological conditions, *etc.,* [2].

The heart works actively, steadily and also establishes an interaction with the brain. This interconnection is termed as neurocardiology [3]. It plays a pathophysiological role in which the heart sends the information to the brain *via* afferent nerve for maintaining homeostatic equilibrium [4]. This heart-brain system consists of compound ganglia altogether termed as ganglionic plexus. It contains intrinsic cardiac ganglia, which have afferent nerve fibers for receiving information, local circuit ganglia are the interneuron and efferent ganglia which transmit a signal through sympathetic and parasympathetic neurons [5]. The increasing scientific evidence about brain-heart interactions is playing a key role in the management of cardiovascular diseases. The heart also possesses an intrinsic cardiac nervous system that processes the sensory information from other organs, blood vessels, and even from the heart to maintain cardiac activity [6]. Though the elaborated information about the properties of the intrinsic cardiac nervous system is not available, this information is considered important during cardiac clinical practices.

Since the past decades, researchers have analyzed the interconnection between the death of individuals due to cardiovascular problems and involvement of the ANS in the regulation of cardiac activity. It has also been observed that cardiac activities are constantly controlled by the autonomic nervous system (ANS) that influences the changes in time per heartbeat. Hence, heart rate variation also assesses the role of the ANS in cardiac activity [7].

2. HEART RATE VARIABILITY (HRV) AND INVOLVEMENT OF THE NERVOUS SYSTEM

Cardiac function is not only to circulate blood throughout the body but also to collaborate with other body functions. In this activity, HRV plays an important role. Various factors influence the cardiac rhythm and cause variation between two consecutive heartbeats. The cardiac output is regulated by the central nervous system by the neural and endocrine pathways.

HRV is also called variability in beat-by-beat heart period, which is an intrinsic attribute of cardiac functioning [8]. Heart rate can be defined as the number of heartbeats in a minute and HRV is the variation among heartbeat in a specific period. Variability is accessed by analyzing the shuffling of heartbeat in 24 hours. It has been noticed that the heartbeat frequency is not constant. It may be assumed that if we assess the heartbeats at the rate of 60 beats per minute (BPM), then actually, it does not reflect a rate of one second for one beat while mathematically, it must be one beat every second. It is suggested that there is a variation of time in heartbeats and it may be like 0.9 seconds, 1.2 seconds, or more among heartbeats.

HRV and heart rate are two different indicators, in which heart rate is calculated by counting heartbeats in a minute while HRV changes in time when a single heartbeat is recorded. There is a variety of different HRV metrics. It has been found that healthy adult populations have a mean value of 42 milliseconds within a range of 19-75 milliseconds and it may be 120 milliseconds in athletes [9].

HRV is the assessment of the electrical activity of the heart through an electrocardiogram (ECG or EKG) test. It is observed that heart rate may be high or low depending on physical activities, stress conditions, and emotions of individuals. Thus, HRV may be recognized as the response of the heart towards any kind of stimuli so that it compensates the situations accordingly, and thus, its variation may be used as warning signs of cardiac diseases [10].

HRV is one of the approaches by which the state of neurocardiac physiology can be assessed. It also evaluates the factors which influence heartbeats. Including this, information about the time interval between heartbeats may suggest how internal and external needs can be achieved [11, 12]. It is also found that there are various pathological and non-pathological conditions like cardiac disease, mood disorder conditions that can influence HRV, and thus HRV may be recognized as an indicator of health [11, 12]. HRV is also considered useful in finding the physiological responses to both acute and chronic stress factors. Thus, regulation of heart rate in different situations is the dealing among the physical, mental and cognition state of an individual. Therefore, it may be assumed that HRV can be one of the measures to find out the body's ability to respond to internal and external stimuli to maintain equilibrium [10, 13]. Thus, HRV may also be used to access cardiac adaptability under the influence of stimuli. However, before assessing the adaptability process firstmost it is important to know the HRV influencing variable (physiological or environmental) [14]. HRV may be the biomarker of various conditions such as vascular tone, which is an important factor to maintain blood pressure, cardiac function and gut function, *etc.,* [12, 15].

The HRV not only expresses the state of the ANS but also estimates the vagal nerve and sympathetic nerve activities [16]. It has been reported that cardiac vagal control has an opposing effect on the sinoatrial node of the heart. The cardiac vagal activity is regulated by neurotransmitters such as Acetylcholine by binding to the receptors (Muscarinic and nicotinic). These receptors act differently and their function can also be influenced or suppressed by the use of drugs. In-

cluding this, hereditary trait also plays a role in the regulation of cardiac vagal system [17].

2.1. HRV and Physiological Foundation

Continuously alteration and regulation of the heart rate and its rhythm are made by ANS [18] Vagus nerve of Parasympathetic Nervous System (PNS) innervates the sinoatrial, atrioventricular node and also myocardium of the heart. ECG recording is one of the most common methods for assessing the heart rate. The activation of parasympathetic nervous system results in acetylcholine release, due to which the duration between R-R interval increases and heart rate decelerate [19]. On the contrary, Sympathetic Nervous System (SNS) increases the secretion of catecholamine by the synapses, which accelerate the heart rate and its contractility. Comparative to the action of acetylcholine, catecholamines action is slowed down, which leads to impediment in sympathetic stimulation and by 5 second heart rate changes. By the difference among neurotransmitters of the sympathetic nervous system and parasympathetic nervous system, it has been identified that the impact of every ANS arm is same and symmetrical but presents the variation in time frequencies of action and overlapping [20].

2.2. Methods of HRV Analysis

ANS modulation on the heart can be analyzed from the ECG processing [21]. Among the several techniques, which are grounded recently for this assessment, it was found that HRV is one of the most noninvasive and fast ways, which is most commonly used for analyzing the most reproducible and unfailing data about autonomic modulation of the heart rate [22].

2.2.1. Time Domain Methods

Time domain measure is one of the simplest methods to evaluate the variation in heart rate. This method is conducted either by calculating intervals among successive normal complex or by determining the heart rate at any specific point in time. For the determination of instantaneous heart rate or normal to normal (NN) interval (QRS complex intervals due to depolarization of sinus node), QRS complex in continuous ECG record is identified. Factors that have to be calculated in this method are heart rate mean, heart rate difference in day and night difference among shortest and longest NN interval, and also by assessing respiration, drug like phenylephirine infusion impact the heart rate. By detecting the differences among cycle length or heart rate, these differences can be assessed [23].

2.2.2. Geometrical Methods

Geometric pattern can also be derived from the series of NN intervals. In this method, three general approaches are used: i) geometric pattern measurement ii) interpolation of geometric pattern by the use of shape which is mathematically defined iii) various pattern- based categories of the geometric shape, shows the various categories of HRV. Measurements of NN interval sequence or discrete scale conversion is the requirement of the geometric methods, which allows the creation of histogram.

The integral of the density distribution is the measurement of HRV triangular index, which is divided by density distribution in maximum. On a discrete scale, the value is calculated by: (NN interval in total)/ (modal bin's NN interval). The baseline width of the calculated distribution is the Triangular Interpolation of NN interval histogram (TINN). TINN and Computing HRV triangular index reflect total HRV measured in 1 day and powered by the higher frequencies. The disadvantage of this method is the requirement of the total number of NN interval so that geometric patterns can be constructed, whereas the relative insensitivity towards the analytical quality of the NN interval series is the major advantage [24].

2.2.3. Statistical Method

Statistical time domain can be calculated from the series of instantaneous heart cycle intervals or heart rate specifically which are recorded over a period of 24 hours. This can be classified among two groups: a) those resultant from calculation from instantaneous heart rate or NN interval directly ii) resultant of the difference of NN intervals. By the use of ECG recording analyses or by analyzing smaller segments of the recording period, this variable can be derived. Furthermore, a comparison of HRV while different activities like sleep, rest *etc.*, can be calculated.

Calculation of square root of the variance, that is the standard Deviation of NN interval (SDNN), is the easiest variable. Every cyclic component, which is the cause for variability in the recording period represented by SDNN, shortest and shortest cycle length can be measured by SDNN in a decrease monitoring period. It has also been observed that with the increased period of analyses, total variance of HRV recording also increases [25]. Hence, SDNN relies upon the time duration of recording; it cannot be considered as well defined statistical quantity. Therefore, SDNN values collected from the various situation recording should not be compared while for the calculation of the SDNN, standardize time duration of the recording should be considered.

2.2.4. Frequency Domain Methods

Information about the variance (power) spread as a function of frequency can be collected by the analyses of Power Spectral Density (PSD). Parametric and non parametric methods can be used for the determination of the PSD. In this, both the methods give analogous result. Advantages of parametric methods are: a) even on a small number of samples, an accurate PSD can be calculated; b) independent of preselected band of frequency can be distinguished by smoother spectral components. Advantages of non-parametric methods are: a) use of algorithm simply; b) processing seed is high. Parametric demands evidence about the suitability of the selected model and it is a complex process, while non parametric method FFT (Fourier transformation) is a rapid and easy method to perform [26].

RR intervals that are kept in the computer are converted into bands with varying spectral frequencies at the time of

using the FFT method. Moreover, by diving the finding by obtained mean of RR intervals length, collected reflections can be changed into Hz (Hertz).

Frequency band between 0-0.5Hz of power spectrum can be categorized into four bands [26]:

A. High frequency (HF) (0.15-0.4 Hz)

B. Low frequency band (LF) (0.04-0.15 Hz)

C. Very low frequency band (VLF) (0.003-0.04Hz)

D. Ultra low frequency band (ULF) (<0.003 Hz)

VLF, HF and LF are the characteristics of short term spectral, which are recorded for 5-10 minutes, whereas in the long term recording, these three components and ULF component are also included.

The sum of the four spectral bands LF, HF, ULF and VLF and variance is the total power of RR interval variability. Vagal modulation is used to define the HF component and sympathetic and parasympathetic nervous system modulates the LF components. Therefore, sympathetic activity can be due to the consequences of the increase LF component, antagonistically reduction in LF power can lead to the beta adrenergic blockade. The global sympatho-vagal balance can be represented by the ratio between LF and HF components and this can also be used for determining this balance. In healthy adult, during rest ratio (LF/HF) is 1:2. Furthermore, the long period of rhythms and circadian, neuroendocrine rhythm is reflected by the component VLF and ULF, respectively [26].

2.2.5. Fractal Analysis (Non Linear Methods) of HRV Measurement

Fractal geometry and Chaos theory is the base of the non-linear methods. The study of non- linear, non periodic system and multivariable is referred to as Chaos [27]. This theory may be used in understanding the dynamics of heart rate, considering that heart rate in healthy individual is extent chaotic up to some extent and slightly irregular. In this method, parameters that are used to calculate HRV properties are Coarse Graining Spectral Analyses (CGSA), 1/f scaling of Fourier spectra H scaling exponent [28]. Recent studies suggested that abnormal patterns of RR fluctuation can be detected more efficiently by fractal analysis for standard HRV measurement comparison.

2.3. Importance of HRV

HVR is one of the means to find out the state of the ANS. The variation between heartbeat is low in sympathetic activation and high in parasympathetic mode. It has been observed that low HRV indicates cardiovascular diseases such as hypertension, whereas high HRV shows higher cardiac fitness. Knowing about HRV is one of the best ways to assess the impact of various factors such as; environment, emotion, thoughts, feeling, etc, on the nervous system and how the nervous system responds accordingly [29]. HRV can also suggest the fetal distress condition during labor and it is subjected to uterine contractions [30].

As per the changes in the physiology of vital organs, the sympathetic and parasympathetic systems maintain the state of equilibrium. ANS sends the message through stellar ganglion and vagus nerve to the sinoatrial node of the heart to stimulate the heart variability in the normal range, which can be assessed by evaluating HRV. The sensory neurons of the peripheral nervous system send the signal from the heart (if any variation) to the central nervous system to regulate the ANS to compensate for the condition accordingly [29].

HRV may also give information about cycle length dependency. Whenever heart rate increases, HRV decreases because of the insufficient period for the heartbeat. In the geriatric group, elderly persons with cardiac diseases like ischemia and heart attack *etc.,* or any pathological condition may result in decreased HRV at high heart rates [31]. Significant knowledge about all the influencing factors for HRV like physiological, environmental or genetic, plays an important role not only in clinical diagnosis but also in therapeutic purpose [14].

2.4. Brain and Heart Communication

It is studied that HRV is the result of brain and heart communication that how ANS regulates the cardiac function under different circumstances to maintain a balance between internal and external stimuli. Communication between the heart and brain is the neurological pathway that is responsible for producing HRV [3, 4]. The brain-heart is universally called an intrinsic cardiac nervous system. It has a complex structure consisting of ganglions, neurotransmitters, supportive cells and proteins. The nervous system regulates cardiac functions by sending signals *via* sympathetic and parasympathetic activation. Under the influence of any stimuli which affects the heart's normal physiology (such as; heart rate, rhythm, pressure or any hormonal variation), the sensory neurons immediately send the signals to the cardiac nervous system, which result in sympathetic nervous system activation and send efferent nerve of the ANS through descending pathway to regulate cardiac function accordingly [32].

In this cardiac brain communication, intrinsic nervous system of the heart sends a signal along with the ascending nerve fibers of the vagus nerve and also through the spinal column following the pathway to reach the medulla, hypothalamus, thalamus, amygdala, and then finally to the cerebral cortex for the interpretation.

The brain sends signals from myocardiocytes following the polysynaptic pathway to the ganglion situated in the peripheral area, and then signals further proceed towards preganglionic and premotor neurons. Cardiac activities are regulated by the activation of cardiac reflex such as baroreceptors, chemoreceptors, nasopharyngeal receptors, *etc.*, and also *via* central autonomic responses to stress, physical exercises, sleep cycle *etc.,* [33]. Clinically, it has been observed that chronic neurodegenerative disease may gradually affect the function and even lead to failure of ANS. However, the pathological condition of blood vessels, neurological problems or lesions (inflammation or injury) may induce hyperactivity of ANS [34].

2.5. Sympathetic and Parasympathetic Correlation

Physiology of human body (metabolism, thermoregulation, and cardiac activity *etc.*) is under the influence of ANS. Sympathetic and parasympathetic nervous systems are the two subdivisions of ANS, which works differently in different situations so that they can regulate homeostasis. The sympathetic system gets activated under stressful conditions (fear, fight or flight) and causes elevated heart rate, increase sweat production whereas parasympathetic acts at rest and digestion state which results in a decrease in cardiac rate and maintain homeostasis [35]. During sympathetic activation, stress hormone production is stimulated, which results in high cardiac output and low HRV while the parasympathetic system decreases the heart rate and increases the HRV to establish homeostasis once the stressful conditions are over. This interconnection between the two branches of the ANS *i.e.* sympathetic and parasympathetic systems, permits the heart to act in varied conditions and demands.

Sympathetic and parasympathetic nervous systems are antagonist to each other. Under the influence of parasympathetic system, vagus nerve acts as an inhibitor of heart rate. Moreover, vagus nerve initially acts upon the sinoatrial (SA) node *i.e.* pacemaker of the heart, to initiate a conduction system while the sympathetic nervous system targets the atrioventricular (AV) node for the forceful contraction of heart chambers [36]. Hence, sympathetic activation alters the inhibitory function of the vagus nerve and increases heart rate while parasympathetic activates vagal inhibition property results in low heart rate.

The parasympathetic nerve (vagus) includes both afferent and efferent nerve fibers, but the majority of the fibers are afferent, which are responsible for sending the signals from the heart to the brain. After receiving the information from the heart, central nervous system sends the efferent nerve to the pacemaker (SA node), then the AV node, and also to the other parts of the heart [1]. It has been observed that for performing function effectively and properly under normal circumstances, the cardiac's intrinsic nervous system works independently. It has been found out that signal molecules do play an important role in this signaling. GABA has predominantly been reported as the key molecule. It is involved in the regulation of blood pressure by adjusting heart rate [37]. It is reported that GABA activation causes the inhibition of the vagus nerve and exhibit reduced parasympathetic effect on the heart [38].

Cardiac ganglia that are present externally in the thoracic cavity have direct and indirect connectivity with the human system. They are directly interacting with the lungs and esophagus while indirect interaction takes place through the spinal cord to the other body parts like skin and arteries *etc.*

2.6. Significance of HRV Assessment

HRV analysis is not only used as a neuro-cardio parameter but also has a vital role in evidence-based practice of medicine. HRV is one of the health indicators used worldwide [39]. It is important to assess the variation in heart rate for evaluating cardiac conditions by studying the fluctuation in RR intervals. HRV accessment is mainly done by the linear time based method, non linear method, frequency- based method (Table **1**) [40]. The assessment of HRV is coorelated with many factors. Though non linear assessment is conducted comparatively less than the linear method, it contributes additional information on linear method and indicates that hormonal variation and thermal fluctuation influence HRV [40, 41]. In the linear time based method, cardiac activity is recorded between two variables *i.e.* time and frequency [42]. The nonlinear method is also helpful in the prognosis of heart failure patients, but because of lack of reproducibility, it is less in use. On the basis of the duration of data records, HRV can be evaluated by short term and long term HRV analysis method [43].

The HRV accessment is also being used in clinical studies. It is found that reduced variability is used as a marker of enhanced pathology and also suggests the conditions of morbidity and mortality. HRV assessment has the potential to be helpful in trauma as a tool of initial patient evaluation, and regular monitoring of patients with critical injury [44].

However, there are technical limitations and shortage of standard values that hinder its clinical applicability in trauma. It has been observed that for accurate HRV evaluation, data should be collected on healthy beat to beat intervals of heart. Murmur beat such as extra heart sound or missing sound should be excluded otherwise, bias can occur in HRV analysis criteria. However, any defective beats can be rectified by treating the pathological conditions before proceeding with HRV assessment [45, 46]. In addition, ECG records suggest two main important heart conditions; firstly it confines about the initiation of ectopic or murmur heartbeats or arrhythmic condition. On the other hand, it analyzes the respiratory rate [47, 48].

3. FACTORS AFFECTING HRV

HRV may be stated as adaptation or response of the heart to any provided stimuli. Various factors have been identified which stimulate HRV as physiological factors, environmental factors and pathological factors *etc.,* (Fig. **1**). Now-a-days, HRV is also being regarded as a health indicator [14].

The investigators have grouped the factors affecting HRV into five categories like; lifestyle factors, environmental factors, physiological and pathological factors, non-modifiable factors [14]. Including this categorization, some other types of factors affecting HRV are also identified, such as; age, gender, genetic, chronic health conditions and lifestyle factors (like nutrition, alcohol circadian rhythm, and stress *etc.,*) [49]. The role of many factors is discussed as follows;

Table 1. Heart rate variability association with mortality rate (Singh *et al.* 2018).

S. No.	HRV Parameter	Monitoring Method	Result / Conclusion
1.	SDNN, LF and HF (standard deviation of NN interval, low frequency power, high frequency power)	Resting ECG, 8 min	Increased risk of sudden death with reduced LFP (RR 2.8,95%-CI(1.2-6.8),p=0.02)
2.	SDNN, rMSSD, VLF, LF, HF, LF/HF, TP (standard deviation of NN interval, low frequency, high frequency, root mean square of the differences in successive R-R interval, very low frequency power, low frequency power, high frequency power, low frequency to high frequency power ratio, total power)	Resting ECG	SDNN(28ms *versus* 36ms,p=0.037), rMSSD(28ms *versus* 29ms, p=0.007),and In HF (4.7ms *versus* 5.5 m, p= 0.008) are depressed in patients with FRS>10%
3.	SDNN, rMSSD, SDSD, pNN50 (standard deviation of NN interval, root mean square of the differences in the successive, standard deviation of absolute differences between successive interval, percentage of RR interval that differ by 50ms)	Resting ECG, 2 min	Enhanced risk of all- cause mortality for patients in the lowest quartile of all parameters (RR 1.47- 1.91)
4.	SDNN (standard deviation of NN interval)	Resting ECG, 10 sec	SDNN in the lowest and highest quartiles had increased risk of cardiac mortality; HR 1.8(95% CI91.0-2.3) and 2.3(95% CL(1.3-4.00)respectively
5.	SDNN(standard deviation of NN interval)	Resting ECG, 15-30 sec	SDNN<20 ms associated with increased risk of CHD (RR 2.1, 95%CI(1.1-4.1) and all cause mortality (RR2.1,95% CI (1.4-3.0)

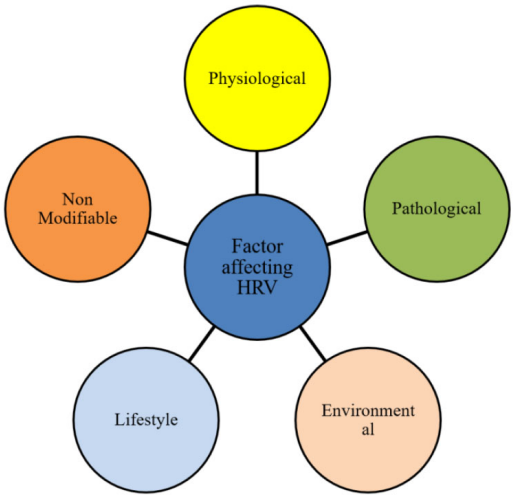

Fig. (1). Different Factors affecting heart rate variability. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.1. Physiological Variable

Physiological factors like age, gender and circadian rhythm, *etc.*, moderately influence HRV. An individual's HRV (at a resting state) is high till age 15 and in older age HRV declines [50]. Physical exercise was also found to be associated with a reduction in HRV [51]. It is also found that the sympathetic and parasympathetic performance of ANS varies in male and female, which results in the gender-based difference in HRV and these variation decreases by the age of 50 [49]. The circadian cycle also affects the HRV as it declines in day-time and high at night [52].

The ANS not only regulates HRV but also it acts upon the inflammatory process caused by any pathogens, signal sends to the brain about invasion of causative agent *via* vagus nerve. It has been studied that cholinergic anti-inflammatory pathway controls the immune response against injury or pathogen. Therefore, lack of cholinergic reflexes or pro-inflammatory cytokines for a long duration resulted in the reduction of HRV, causing cardiovascular diseases [53].

It is observed that heart rate increases in inhalation and decreases in the exhalation of air. Thus, while analyzing the HRV, it is important to mention that correlation between heart rate and respiration, both factors influence HRV [54].

3.2. Pathological Variable

It has been found in many studies that pathological conditions (such as; inflammation and infection) decrease the HRV [13, 51, 55]. It has been observed that HRV can be one of the measures to rule out the effect of pathological conditions (viral infection, sepsis, inflammation, *etc.,*) on cardiac function and inadequate response to maintain homeostasis may cause immunodeficiency and result in infection or cancer [56]. The C- reactive protein (CRP), a pentameric protein that has a liver origin, is found in high amount in circulatory fluid in case of any inflammatory process followed by the secretion of interlukin-6 secreted by macrophages and T cells. The primary function of this protein is to improve the antibodies and phagocyte function. Increased level of CRP is related to cardiovascular and metabolic disorders [11, 57]. Therefore, it is important to consider inflammation and HRV to rule out pathological conditions like hypertension, and diabetes *etc.,* [58]. Increased heart rate may also result in increased cardiac output and decreased afterload because of lack of blood vessel's elasticity and may elevate or decrease cardiac muscle's contractility [51, 59]. The parasympathetic nervous system influences the parasympathetic cardiac activity and responsible for reduced heart rate frequency [60].

3.3. Environmental Factor

Environmental factors also influence HRV [14]. It has been studied that increased social stress and noise increase the HRV whereas a low level of carbon monoxide decreases the HRV. Including this, the effect of temperature on HRV is also found negligible [61]. Researchers have reported that modulation of ANS by genetic and environmental factors [62]. In this study, multivariate statistical analysis was performed using different parameters and it was found that body mass index, coffee consumption, smoking, and chronic diseases are associated with variation in HRV.

3.4. Lifestyle Factor

It has been analyzed that HRV is more in average-to-strenuous physical activities. Habits like alcohol consumption and cigarette smoking also decrease the HRV. Heavy cigarette smoking has been associated negatively with autonomic function [63]. It is suggested that cardiac vagal regulation is reduced by smoking, which may be considered as one of the pathophysiological aspects of smoking [64]. Alcohol consumption and tobacco smoking also affect HRV. The consumption of alcohol is assumed to reduce HRV by stimulation of sympathetic activities and inhibition of the parasympathetic stimulation. The study has revealed that in nondependent users alcohol consumption (1 and 2 standard drink in women and men respectively as daily recommended use) is associated with the rise in HRV while higher alcohol intake is associated with reduced HRV [65]. It may be suggested that in chronic smokers and heavy alcohol drinkers, HRV is decreased, but this condition may be improved by healthily modifying their lifestyle.

3.5. Psychological Factor

It has been observed that HRV can be used as one of the measures to check the level of mental stress. There are many neurological conditions (depression; chronic stress) that may influence the normal physiology of the heart, endocrine system, neurological and muscular system due to the lack of improvement and healing. These factors revealed that the brain and heart are interrelated with each other and any change results in the variation of HRV. Researchers have revealed that anxiety disorders are associated with decreased HRV [66]. Major depression is also associated with reduced HRV [67]. Including this, it has been revealed that untreated, physically healthy patients with major depressive disorder (absence or presence of comorbid anxiety) had reduced HRV [68]. During stressful circumstances, HRV is decreased under the influence of parasympathetic activation [69].

3.6. Genetic Variable

Genetic factors have been found to significantly affect the HRV at the rest and stress conditions. Thus, identification of the genetic factors of HRV may give further information to understand the pathophysiology of the ANS and propose the approaches for its modulation [70]. HRV is observed more in females than males. The impact of the hereditary factors on HRV is considered higher under psychological stress [71]. It was observed that many genetic effects are similar in both the genders and the climatic effect on HRV among people is negligible. Nevertheless, climatic factors have an impact on heart autonomic function, which is regulated by genetic make-up of an individual [72]. In one study, researchers have identified 11 SNPs linked with heart rate and it was found that the HRV reducing allele was associated with increased heart rate. In this study, it was found that genetic variants (RGS6 and GNG 11) affect the activity of G protein heterotrimer in GIRK-channel regulated hyperpolarization of the pacemaker membrane [73]. One study was conducted to evaluate the difference in HRV among black Americans and white Americans and it was revealed that HRV is more in Afro- American than Euro- Americans [74].

4. HRV AND ALTERNATIVE MEDICINE

In the experimental studies, the effect of herbal remedies and placebo pills has been observed and found that herbal remedies are more satisfying than placebo pills. Herbal remedies have a great role in controlling sympathovagal function and also in neuro-cardiac regulation, which results in the decrease of heart rate, thereby, adversely increasing HRV [75]. Acupuncture is one of the most popular carried out therapeutic methods used by the Chinese population. This modality work by implementing on both external and internal environment of the individual to establish a balance among physical, emotional and hormonal demands [76]. ANS is dynamic so that it can respond towards external and internal changes accordingly to sustain equilibrium [77]. Researchers assumed that acupuncture has an impact on the function of ANS and metabolism and this ANS regulation and revitalization of metabolism can be assessed by HRV analysis [78, 79]. Even though acupuncture is well known analgesic for pain, it works by puncturing acupoints by the use of needle. Conversely, how it works in stabilizing homeostasis is not clear, but in one of the reports it is found that acupuncture influences the cardiac vagal activity by increasing its impact and hampering sympathetic performances [80]. Hence, acupuncture modality may be able to alter the HRV on low frequency (sympathetic activity impression) during pathogenic and non-pathogenic conditions [81].

It has been observed that complementary and alternative medicine usage is high and beneficial in health and wellness among cardiac sufferers [82]. It has been found that prolonged psychophysiological stress disturbs the autonomic balance of the nervous system and may lead to physiological and psychological disorders [83]. Yoga, one of the streams of AYUSH modalities, is the alternative treatment of medicine (ayurveda, yoga and naturopathy, unani, siddha and homeopathy system of health care). In yoga modalities, body-mind practices are involved, which aim to maintain the balance between body and mind. It has been found that there is a healthy relationship between yoga and indices of sympathetic and parasympathetic activity like cognitive abilities, baroreflex [84] and emotion regulations *etc.,* and also it helps in treating dysfunctions of autonomic system like depression, hypertension [85], and diabetes, *etc.,* [86]. As it is

found that neural and endocrine pathways are used to regulate the cardiac output by central nervous system. Hence, control on the central nervous system will influence the cardiac output [87]. The yoga practice helps in improving cardiac function and also in modifying the performance of ANS [88-90].

CONCLUSION

Heart is a vital organ that communicates with the brain *via* heart-brain interconnection, which is known as neurocardiology. Heart rate is described as the number of heartbeats in a minute and HRV is the variation among heartbeats in a specific period. Variability is accessed by analyzing the shuffling of heartbeats in 24 hours. It is observed that heartbeat frequency is not constant and HRV is also called as variability in beat-by-beat heart period, which is an intrinsic attribute of cardiac activity. It has been studied that HRV plays a key role in the well being state of an individual. It is the result of the interplay between the sympathetic and parasympathetic systems. Where the sympathetic system enhances HRV and the parasympathetic system reduces the HRV. The high HRV is considered as an indicator of good health. The HRV is influenced by many factors such as physiological, pathological, psychological, lifestyle, environmental, and genetic factors. All of these factors are individually or interconnectedly affecting HRV. Out of these factors, genetic factors also make a remarkable impact on variation in HRV and heart rate which are particular to the stressful conditions.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Authors are thankful to the Karaganda Medical University, Karaganda, Kazakhstan for providing the necessary facilities.

REFERENCES

[1] Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World J Cardiol 2015; 7(4): 204-14. http://dx.doi.org/10.4330/wjc.v7.i4.204 PMID: 25914789

[2] Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012; 2(2): 1143-211. http://dx.doi.org/10.1002/cphy.c110025 PMID: 23798298

[3] van der Wall EE, van Gilst WH. Neurocardiology: close interaction between heart and brain. Neth Heart J 2013; 21(2): 51-2. http://dx.doi.org/10.1007/s12471-012-0369-4 PMID: 23239452

[4] Ritz K, van Buchem MA, Daemen MJ. The heart-brain connection: mechanistic insights and models. Neth Heart J 2013; 21(2): 55-7. http://dx.doi.org/10.1007/s12471-012-0348-9 PMID: 23179612

[5] Birand A. Kalbin içrek gangliyonlanmiş nöral pleksusu. Anadolu Kardiyol Derg 2008; 8(6): 451-4. PMID: 19103543

[6] Kingma JG, Simard D, Rouleau JR. Influence of cardiac nerve status on cardiovascular regulation and cardioprotection. World J Cardiol 2017; 9(6): 508-20. http://dx.doi.org/10.4330/wjc.v9.i6.508 PMID: 28706586

[7] Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput 2006; 44(12): 1031-51. http://dx.doi.org/10.1007/s11517-006-0119-0 PMID: 17111118

[8] Karemaker JM. How the vagus nerve produces beat-to-beat heart rate variability; experiments in rabbits to mimic *in vivo* vagal patterns. J Clin Transl Res 2015; 1(3): 190-204. PMID: 30873454

[9] Biovotion Heart rate variability. Available from: https://biovotion.zendesk.com/hc/en-us/articles/213581885-Heart-Rate-Variability

[10] Chuduc H, NguyenPhan K, NguyenViet K. A review of heart rate variability and its applications. Int J Sci Res 2013; 7: 80-5. http://dx.doi.org/10.1016/j.apcbee.2013.08.016

[11] Jarczok MN, Kleber ME, Koenig J, *et al.* Investigating the associations of self-rated health: heart rate variability is more strongly associated than inflammatory and other frequently used biomarkers in a cross sectional occupational sample. PLoS One 2015; 10(2): e0117196. http://dx.doi.org/10.1371/journal.pone.0117196 PMID: 25693164

[12] Young HA, Benton D. Heart-rate variability: a biomarker to study the influence of nutrition on physiological and psychological health? Behav Pharmacol 2018; 29(2-3): 140-51.

[13] Young H, Benton D. We should be using nonlinear indices when relating heart-rate dynamics to cognition and mood. Sci Rep 2015; 5: 16619. http://dx.doi.org/10.1038/srep16619 PMID: 26565560

[14] Fatisson J, Oswald V, Lalonde F. Influence diagram of physiological and environmental factors affecting heart rate variability: an extended literature overview. Heart Int 2016; 11(1): e32-40. http://dx.doi.org/10.5301/heartint.5000232 PMID: 27924215

[15] Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017; 5: 258. http://dx.doi.org/10.3389/fpubh.2017.00258 PMID: 29034226

[16] Ernst G. Heart-rate variability-more than heart beats? Front Public Health 2017; 5: 240. http://dx.doi.org/10.3389/fpubh.2017.00240 PMID: 28955705

[17] Riese H, Muñoz LM, Hartman CA, *et al.* Identifying genetic variants for heart rate variability in the acetylcholine pathway. PLoS One 2014; 9(11): e112476. http://dx.doi.org/10.1371/journal.pone.0112476 PMID: 25384021

[18] Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. Int J Cardiol 2002; 84(1): 1-14. http://dx.doi.org/10.1016/S0167-5273(02)00057-8 PMID: 12104056

[19] Draghici AE, Taylor JA. The physiological basis and measurement of heart rate variability in humans. J Physiol Anthropol 2016; 35(1): 22. http://dx.doi.org/10.1186/s40101-016-0113-7 PMID: 27680542

[20] Johnston BW, Barrett-Jolley R, Krige A, Welters ID. Heart rate variability: Measurement and emerging use in critical care medicine. J Intensive Care Soc 2020; 21(2): 148-57. http://dx.doi.org/10.1177/1751143719853744 PMID: 32489411

[21] Massaro S, Pecchia L. Heart Rate Variability (HRV) analysis: A methodology for organizational neuroscience. Organ Res Methods 2019; 22(1): 354-93. http://dx.doi.org/10.1177/1094428116681072

[22] Parati G, Mancia G, Di Rienzo M, Castiglioni P. Point: cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol (1985) 2006; 101(2): 676-8. http://dx.doi.org/10.1152/japplphysiol.00446.2006 PMID: 16645191

[23] Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am Heart J 1994; 127(5): 1376-81.

http://dx.doi.org/10.1016/0002-8703(94)90059-0 PMID: 8172068

[24] Copie X, Hnatkova K, Staunton A, Fei L, Camm AJ, Malik M. Predictive power of increased heart rate *versus* depressed left ventricular ejection fraction and heart rate variability for risk stratification after myocardial infarction. Results of a two-year follow-up study. J Am Coll Cardiol 1996; 27(2): 270-6. http://dx.doi.org/10.1016/0735-1097(95)00454-8 PMID: 8557893

[25] Saul JP, Albrecht P, Berger RD, Cohen RJ. Analysis of long-term heart rate variability: methods, 1/f scaling and implications. Computers in Cardiology 1987. Washington, DC: IEEE Computer Society Press 1988; pp. 419-22.

[26] Orini M, Bailón R, Laguna P, Mainardi LT. Modeling and estimation of time-varying heart rate variability during stress test by parametric and non parametric analysis. 2007 computers in cardiology. Durham, NC: IEEE 2007; pp. 29-32.

[27] Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996; 32(2): 208-16. http://dx.doi.org/10.1016/0008-6363(96)00116-2 PMID: 8796106

[28] Yamamoto Y, Hughson RL. Coarse-graining spectral analysis: new method for studying heart rate variability. J Appl Physiol (1985) 1991; 71(3): 1143-50. http://dx.doi.org/10.1152/jappl.1991.71.3.1143 PMID: 1757311

[29] Servant D, Logier R, Mouster Y, Goudemand M. Heart rate variability. Applications in psychiatry. Encephale 2009; 35(5): 423-8. http://dx.doi.org/10.1016/j.encep.2008.06.016 PMID: 19853714

[30] Warmerdam GJJ, Vullings R, Van Laar JOEH, *et al.* Detection rate of fetal distress using contraction-dependent fetal heart rate variability analysis. Physiol Meas 2018; 39(2): 025008. http://dx.doi.org/10.1088/1361-6579/aaa925 PMID: 29350194

[31] McCraty R, Shaffer F. Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med 2015; 4(1): 46-61. http://dx.doi.org/10.7453/gahmj.2014.073 PMID: 25694852

[32] Science of the Heart. Exploring the role of the heart in human performance. An overview of research conducted by the HeartMath Institute. Available from: https://www.heartmath.org/research/science-of-the- heart/

[33] Dampney RA. Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ 2016; 40(3): 283-96. http://dx.doi.org/10.1152/advan.00027.2016 PMID: 27445275

[34] Silvani A, Calandra-Buonaura G, Dampney RAL, Cortelli P. Brain-heart interactions: physiology and clinical implications. Philos Trans- Royal Soc, Math Phys Eng Sci 2016; 374(2067): 20150181. http://dx.doi.org/10.1098/rsta.2015.0181 PMID: 27044998

[35] de Looff PC, Cornet LJM, Embregts PJCM, Nijman HLI, Didden HCM. Associations of sympathetic and parasympathetic activity in job stress and burnout: A systematic review. PLoS One 2018; 13(10): e0205741. http://dx.doi.org/10.1371/journal.pone.0205741 PMID: 30335812

[36] Brack KE, Coote JH, Ng GA. Interaction between direct sympathetic and vagus nerve stimulation on heart rate in the isolated rabbit heart. Exp Physiol 2004; 89(1): 128-39. http://dx.doi.org/10.1113/expphysiol.2003.002654 PMID: 15109218

[37] Ma P, Li T, Ji F, Wang H, Pang J. Effect of GABA on blood pressure and blood dynamics of anesthetic rats. Int J Clin Exp Med 2015; 8(8): 14296-302. PMID: 26550413

[38] Bentzen BH, Grunnet M. Central and peripheral GABA(A) receptor regulation of the heart rate depends on the conscious state of the animal. Adv Pharmacol Sci 2011; 2011: 578273. http://dx.doi.org/10.1155/2011/578273 PMID: 22162673

[39] Litscher G, He W, Yi SH, Wang L. Heart rate variability and complementary medicine. Evid Based Complement Alternat Med 2014; 2014: 395485. http://dx.doi.org/10.1155/2014/395485 PMID: 24688590

[40] Young HA, David B. Heart-rate variability. Behav Pharmacol 2018; 29(2-3): 140-51.

[41] Bai X, Li J, Zhou L, Li X. Influence of the menstrual cycle on nonlinear properties of heart rate variability in young women. Am J Physiol Heart Circ Physiol 2009; 297(2): H765-74. http://dx.doi.org/10.1152/ajpheart.01283.2008 PMID: 19465541

[42] Li K, Rüdiger H, Ziemssen T. Spectral analysis of heart rate variability: time window matters. Front Neurol 2019; 10: 545. http://dx.doi.org/10.3389/fneur.2019.00545 PMID: 31191437

[43] Hayano J, Yuda E. Pitfalls of assessment of autonomic function by heart rate variability. J Physiol Anthropol 2019; 38(1): 3. http://dx.doi.org/10.1186/s40101-019-0193-2 PMID: 30867063

[44] Mark L. Clinical applications of heart rate variability in the triage and assessment of traumatically injured patients. Anesthesiol Res Pract 2011; 2011: 416590.

[45] Lippman N, Stein KM, Lerman BB. Comparison of methods for removal of ectopy in measurement of heart rate variability. Am J Physiol 1994; 267(1 Pt 2): H411-8. PMID: 7519408

[46] Järvelin-Pasanen S, Sinikallio S, Tarvainen MP. Heart rate variability and occupational stress-systematic review. Ind Health 2018; 56(6): 500-11. http://dx.doi.org/10.2486/indhealth.2017-0190 PMID: 29910218

[47] Bailón R, Sörnmo L, Laguna P. A robust method for ECG-based estimation of the respiratory frequency during stress testing. IEEE Trans Biomed Eng 2006; 53(7): 1273-85. http://dx.doi.org/10.1109/TBME.2006.871888 PMID: 16830932

[48] O'Brien C, Heneghan C. A comparison of algorithms for estimation of a respiratory signal from the surface electrocardiogram. Comput Biol Med 2007; 37(3): 305-14. http://dx.doi.org/10.1016/j.compbiomed.2006.02.002 PMID: 16777085

[49] Sammito S, Böckelmann I. Factors influencing heart rate variability. ICF Journal 2016; 6: 18-22. http://dx.doi.org/10.17987/icfj.v6i0.242

[50] Voss A, Schulz S, Schroeder R, Baumert M, Caminal P. Methods derived from nonlinear dynamics for analysing heart rate variability. Phil Trans A Maths Phys Eng Sci 2009; 367(1887): 277-96. http://dx.doi.org/10.1098/rsta.2008.0232

[51] Bravi A, Green G, Herry C, *et al.* Do physiological and pathological stresses produce different changes in heart rate variability? Front Physiol 2013; 4: 197. http://dx.doi.org/10.3389/fphys.2013.00197 PMID: 23908633

[52] Fagard RH. A population-based study on the determinants of heart rate and heart rate variability in the frequency domain. Verh K Acad Geneeskd Belg 2001; 63(1): 57-89. PMID: 11284389

[53] Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev 2012; 36(2): 747-56. http://dx.doi.org/10.1016/j.neubiorev.2011.11.009 PMID: 22178086

[54] Perry S, Khovanova NA, Khovanov IA. Control of heart rate through guided high-rate breathing. Sci Rep 2019; 9(1): 1545. http://dx.doi.org/10.1038/s41598-018-38058-5 PMID: 30733480

[55] Papaioannou V, Pneumatikos I, Maglaveras N. Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: current strengths and limitations. Front Physiol 2013; 4: 174. http://dx.doi.org/10.3389/fphys.2013.00174 PMID: 23847549

[56] Mellemkjaer L, Hammarstrom L, Andersen V, *et al.* Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol 2002; 130(3): 495-500. http://dx.doi.org/10.1046/j.1365-2249.2002.02004.x PMID: 12452841

[57] Dehghan A, Kardys I, de Maat MP, *et al.* Genetic variation, C-reactive protein levels, and incidence of diabetes. Diabetes 2007; 56(3): 872-8. http://dx.doi.org/10.2337/db06-0922 PMID: 17327459

[58] Kudat H, Akkaya V, Sozen AB, *et al.* Heart rate variability in diabetes patients. J Int Med Res 2006; 34(3): 291-6. http://dx.doi.org/10.1177/147323000603400308 PMID: 16866023

[59] Vincent J-L. Understanding cardiac output. Crit Care 2008; 12(4): 174. http://dx.doi.org/10.1186/cc6975 PMID: 18771592

[60] Carter R III, Hinojosa-Laborde C, Convertino VA. Sex compari-

sons in muscle sympathetic nerve activity and arterial pressure oscillations during progressive central hypovolemia. Physiol Rep 2015; 3(6): e12420. http://dx.doi.org/10.14814/phy2.12420 PMID: 26109186

[61] Schnell I, Potchter O, Epstein Y, *et al.* The effects of exposure to environmental factors on Heart Rate Variability: an ecological perspective. Environ Pollut 2013; 183: 7-13. http://dx.doi.org/10.1016/j.envpol.2013.02.005 PMID: 23477780

[62] Uusitalo AL, Vanninen E, Levälahti E, Battié MC, Videman T, Kaprio J. Role of genetic and environmental influences on heart rate variability in middle-aged men. Am J Physiol Heart Circ Physiol 2007; 293(2): H1013-22. http://dx.doi.org/10.1152/ajpheart.00475.2006 PMID: 17400723

[63] Cagirci G, Cay S, Karakurt O, *et al.* Influence of heavy cigarette smoking on heart rate variability and heart rate turbulence parameters. Ann Noninvasive Electrocardiol 2009; 14(4): 327-32. http://dx.doi.org/10.1111/j.1542-474X.2009.00321.x PMID: 19804508

[64] Bodin F, McIntyre KM, Schwartz JE, *et al.* The association of cigarette smoking with high-frequency heart rate variability: an ecological momentary assessment study. Psychosom Med 2017; 79(9): 1045-50. http://dx.doi.org/10.1097/PSY.0000000000000507 PMID: 28731984

[65] Karpyak VM, Romanowicz M, Schmidt JE, Lewis KA, Bostwick JM. Characteristics of heart rate variability in alcohol-dependent subjects and nondependent chronic alcohol users. Alcohol Clin Exp Res 2014; 38(1): 9-26. http://dx.doi.org/10.1111/acer.12270 PMID: 24117482

[66] Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psychiatry 2014; 5: 80. http://dx.doi.org/10.3389/fpsyt.2014.00080 PMID: 25071612

[67] Koch C, Wilhelm M, Salzmann S, Rief W, Euteneuer F. A meta-analysis of heart rate variability in major depression. Psychol Med 2019; 49(12): 1948-57. http://dx.doi.org/10.1017/S0033291719001351 PMID: 31239003

[68] Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One 2012; 7(2): e30777. http://dx.doi.org/10.1371/journal.pone.0030777 PMID: 22355326

[69] von Thiele U, Lindfors P, Lundberg U. Self-rated recovery from work stress and allostatic load in women. J Psychosom Res 2006; 61(2): 237-42. http://dx.doi.org/10.1016/j.jpsychores.2006.01.015 PMID: 16880027

[70] Singh JP, Larson MG, O'Donnell CJ, Levy D. Genetic factors contribute to the variance in frequency domain measures of heart rate variability. Auton Neurosci 2001; 90(1-2): 122-6. http://dx.doi.org/10.1016/S1566-0702(01)00277-6 PMID: 11485278

[71] Muñoz ML, Jaju D, Voruganti S, *et al.* Heritability and genetic correlations of heart rate variability at rest and during stress in the Oman Family Study. J Hypertens 2018; 36(7): 1477-85. http://dx.doi.org/10.1097/HJH.0000000000001715 PMID: 29557905

[72] Golosheykin S, Grant JD, Novak OV, Heath AC, Anokhin AP. Genetic influences on heart rate variability. Int J Psychophysiol 2017; 115: 65-73. http://dx.doi.org/10.1016/j.ijpsycho.2016.04.008 PMID: 27114045

[73] Nolte IM, Munoz ML, Tragante V, *et al.* Genetic loci associated with heart rate variability and their effects on cardiac disease risk. Nat Commun 2017; 8: 15805. http://dx.doi.org/10.1038/ncomms15805 PMID: 28613276

[74] Wang X, Thayer JF, Treiber F, Snieder H. Ethnic differences and heritability of heart rate variability in African- and European American youth. Am J Cardiol 2005; 96(8): 1166-72. http://dx.doi.org/10.1016/j.amjcard.2005.06.050 PMID: 16214458

[75] Li Z, Snieder H, Su S, *et al.* A longitudinal study in youth of heart rate variability at rest and in response to stress. Int J Psychophysiol 2009; 73(3): 212-7. http://dx.doi.org/10.1016/j.ijpsycho.2009.03.002 PMID: 19285108

[76] Vanderploeg K, Yi X. Acupuncture in modern society. J Acupunct Meridian Stud 2009; 2(1): 26-33. http://dx.doi.org/10.1016/S2005-2901(09)60012-1 PMID: 20633471

[77] Collet C, Di Rienzo F, El Hoyek N, Guillot A. Autonomic nervous system correlates in movement observation and motor imagery. Front Hum Neurosci 2013; 7: 415. http://dx.doi.org/10.3389/fnhum.2013.00415 PMID: 23908623

[78] Knardahl S, Elam M, Olausson B, Wallin BG. Sympathetic nerve activity after acupuncture in humans. Pain 1998; 75(1): 19-25. http://dx.doi.org/10.1016/S0304-3959(97)00197-8 PMID: 9539670

[79] Anderson B, Nielsen A, McKee D, Jeffres A, Kligler B. Acupuncture and heart rate variability: a systems level approach to understanding mechanism. Explore (NY) 2012; 8(2): 99-106. http://dx.doi.org/10.1016/j.explore.2011.12.002 PMID: 22385564

[80] Wang JD, Kuo TB, Yang CC. An alternative method to enhance vagal activities and suppress sympathetic activities in humans. Auton Neurosci 2002; 100(1-2): 90-5. http://dx.doi.org/10.1016/S1566-0702(02)00150-9 PMID: 12422965

[81] Chung JWY, Yan VCM, Zhang H. Effect of acupuncture on heart rate variability: a systematic review. Evid Based Complement Alternat Med 2014; 2014: 819871. http://dx.doi.org/10.1155/2014/819871 PMID: 24693326

[82] Bahall M. Complementary and alternative medicine usage among cardiac patients: a descriptive study. BMC Complement Altern Med 2015; 15: 100. http://dx.doi.org/10.1186/s12906-015-0610-y PMID: 25888160

[83] Ginty AT, Kraynak TE, Fisher JP, Gianaros PJ. Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. Auton Neurosci 2017; 207: 2-9. http://dx.doi.org/10.1016/j.autneu.2017.03.003 PMID: 28391987

[84] Bowman AJ, Clayton RH, Murray A, Reed JW, Subhan MM, Ford GA. Effects of aerobic exercise training and yoga on the baroreflex in healthy elderly persons. Eur J Clin Invest 1997; 27(5): 443-9. http://dx.doi.org/10.1046/j.1365-2362.1997.1340681.x PMID: 9179553

[85] Hagins M, States R, Selfe T, Innes K. Effectiveness of yoga for hypertension: systematic review and meta-analysis. Evid Based Complement Alternat Med 2013; 2013: 649836. http://dx.doi.org/10.1155/2013/649836 PMID: 23781266

[86] Tyagi A, Cohen M. Yoga and heart rate variability: A comprehensive review of the literature. Int J Yoga 2016; 9(2): 97-113. http://dx.doi.org/10.4103/0973-6131.183712 PMID: 27512317

[87] Manuel J, Färber N, Gerlach DA, *et al.* Deciphering the neural signature of human cardiovascular regulation. eLife 2020; 9: e55316. http://dx.doi.org/10.7554/eLife.55316 PMID: 32720895

[88] Vinay AV, Venkatesh D, Ambarish V. Impact of short-term practice of yoga on heart rate variability. Int J Yoga 2016; 9(1): 62-6. http://dx.doi.org/10.4103/0973-6131.171714 PMID: 26865773

[89] Nivethitha L, Mooventhan A, Manjunath NK. Effects of various *Prāṇāyāma* on cardiovascular and autonomic variables. Anc Sci Life 2016; 36(2): 72-7. http://dx.doi.org/10.4103/asl.ASL_178_16 PMID: 28446827

[90] Muralikrishnan K, Balakrishnan B, Balasubramanian K, Visnegarawla F. Measurement of the effect of Isha Yoga on cardiac autonomic nervous system using short-term heart rate variability. J Ayurveda Integr Med 2012; 3(2): 91-6. http://dx.doi.org/10.4103/0975-9476.96528 PMID: 22707866