

Heart Rate Variability (HRV)

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Abstract

Heart rate is mainly determined by pacemaker current generated in the SA node. It, in turn, is regulated by autonomic nervous system. Sympathetic stimulation enhances chronotropic, ionotropic and dromotropic activity via α and β receptor activation whereas, parasympathetic stimulation causes reverse effect on heart via the M2 receptors. Varied input from these two branches of the ANS produces change in heart rate. So, HRV, therefore, is the change in the time interval between two consecutive heartbeats. In other words, HRV is the time difference between a given heart beat to the mean duration of heartbeat.

Like all other organs of the body, heart is also susceptible to aging and diseases. These conditions influence heart rate and also HRV.

Today, HRV has invited much investigation and debate. Electronic databases Google Scholar, IMSEAR (Index Medicus for South-East Asia Region), Scopemed and MEDLINE/ PubMed were extensively explored with key words "HRV" or "Heart Rate Variability" from earliest possible date (1973) to December, 2016 and the available information summarized. Different aspects of HRV have been covered including historical background, HRV Analysis Methods, Interpretation of HRV, software's used for HRV recording, importance of HRV measurement, HRV in varying conditions, drugs etc.

HRV offers a relatively simple, well-tolerated, and inexpensive method for studying physiological and pathophysiological processes in a noninvasive manner. However, there are several important challenges in this area of study. There are a number of confounding variables which contribute to HRV data collection and interpretation open to question. Again, one should not compare one's HRV with others, since HRV is affected by numerous internal and external factors, namely, age, lifestyle, hormones, body functions etc.

Keywords: Heart rate; Respiratory Sinus Arrhythmias; Cardiac diseases; Medications

Introduction

Heart rate is mainly determined by pacemaker current generated in the SA node [1]. It is regulated by ANS, which is mediated through nucleus tractus solitarius (NTS) situated in the brainstem (medulla). NTS collects sensory information from chemoreceptors, baroreceptors, muscle afferents, circulating hormones [2] and send autonomic (involuntary) control to heart and blood vessels via sympathetic and parasympathetic nerves. Sympathetic stimulation enhances chronotropic, ionotropic and dromotropic activity via α and β receptor activation whereas, parasympathetic stimulation causes reverse effect on heart via the M2 receptors. Variation in the output of these two branches of the autonomic system produces variability in chronicity of the heart [3,4]. Thus, this variability in heart rate is a physiologic phenomenon and is a reflection of the cardiac modulation by the ANS [5]. Lately, prefrontal cortical activities have also been linked to modulate heart rate [6].

So, HRV is a variation in the time interval between heartbeats. In other words, HRV is the time difference between a given heart beat to the mean duration of heartbeat. It is different from Heart beat rate. If

heart beat rate is 60 beats per minute, each heart beat may not have precisely occurred in each second. It may be such that one heart beat might have occurred at 960 ms and the other at 1112 ms. Difference of each with the "mean value" say 1000 ms gives HRV of 40 ms and 12 ms respectively for those two beats. HRV, thus, refers to beat-to-beat changes in the heart rate [7].

Other names of HRV are inter-beat intervals, R-R intervals, N-N intervals, heart period variability, RR variability, cycle length variability etc. This variability is perfectly normal and is, in fact, desirable. If the heartbeat intervals are constant, HRV is considered to be low; and if the length varies, then HRV is considered to be high [8].

Like all other organs of the body, heart is also susceptible to aging and diseases. These conditions influence the heart rate and also the heart rate variability. This, variation in HRV may point out current disease or impending cardiac and other systemic diseases. Thus, measurement of HRV offer a prognostic plus diagnostic tool in different forms of illnesses [9-13].

Today, HRV has become the subject of active investigation and debate [14,15]. So, this is the authors' endeavor to summarize an extensive literature review on HRV and its potential uses presented in different electronic publications.

Materials and Methods

Electronic databases Google Scholar, IMSEAR (Index Medicus for South-East Asia Region), Scopus and MEDLINE/ PubMed were extensively explored with terms “HRV” or “Heart Rate Variability” from earliest date (1973) to December of 2016. Articles written in any language especially those published in contemporary years were given priority. For articles published in other languages than English, only abstracts were reviewed.

Discussion

Historical background

In 1733, the Rev. Stephen Hales reported for the first time that beat-to-beat heart rate interval and blood pressure measured from arteries vary during the respiratory cycle [16]. After 100 years, Carl Ludwig used kymograph to record the first periodic changes in the amplitude and time of the pressure waves which varied along with respiration. He observed that pulse interval elevated during inspiration and decreased during expiration, which was the first documented report which later was known as the Respiratory Sinus Arrhythmia (RSA) [17].

With advent ECG, it became possible to detect beat-to-beat variations in the cardiac rhythm. The clinical importance of HRV was identified in 1963, when investigators found that just earlier to fetal death, variations in beat-to-beat length were detectable even prior to the variations in the heart rate itself. Again, HRV was reported to have prognostic value in 1987 since decreased HRV was correlated with decreased survival in myocardial infarction [18].

HRV Analysis Methods

There are different ways by which HRV can be analyzed. More commonly it can be measured in two ways i.e. as the alterations in time between two serial R waves on an ECG (“Time domain measures”) or as breaking down of the wave form of ECG-RR intervals into frequency power bands using spectral analysis [19,20].

Time-domain:

- SDNN (standard deviation of RR intervals), is often calculated in a 24-hour duration. It represents total alteration.
- SDANN (standard deviation of the average RR intervals), is calculated usually for 5 minutes.
- RMSSD (Root Mean Square of Successive Differences), the square root of the mean of the squares of the successive differences between adjacent RRs.
- SDSD (Standard Deviation of Successive Differences), measures the standard deviation of the successive differences between adjacent RRs.
- NN50, the number of pairs of successive RRs that differ by >50 ms.
- pNN50, the proportion of NN50 divided by total number of RR
- NN20, the number of pairs of successive RRs that differ by >20 ms.
- pNN20, the proportion of NN20 divided by total number of RRs [4].

Among them, the most frequently used time-domain measures are average SDNN and RMSSD. All time domain measure could be affected by artifacts and outliers, therefore, these should be carefully eliminated. This also is derived by geometric or graphic methods, plotting triangular index. But, this method is highly not affected by

artifacts and ectopic beats as these are left out of the triangle and also requires reasonable number of NN intervals to generate it. Time domain measures are simple to compute but lack the ability to discriminate between different components of ANS on HRV.

Frequency-domain: Frequency domain measures use bands of frequency and then count number of RR intervals that match the bands. For 2–5 mins recording, three main peaks are recognized i.e. Very low frequency (VLF) <0.04 Hz, Low frequency (LF), 0.04 – 0.15 Hz, and High frequency (HF) 0.15 – 0.4 Hz. A fourth peak, Ultra-low frequency (ULF) 0.003–0.04 Hz, is generated if measured for 24 hours. It was the Task Force analysis which split heart rhythm oscillations into those four frequency bands. It also stated that the analysis must be done for five minute segments [21].

Power spectral density (PSD) is another method of analysis which gives fundamental information on the power distribution. Discrete Fourier transform is one of the most commonly used PSD methods whereas, Lomb–Scargle (LS) periodogram is one of the most appropriate PSD estimation method [22].

Non-linear methods: There is increasing evidence to suggest that the heart is not a periodic oscillator under normal physiologic conditions [23] and the commonly employed moment statistics of HRV may not be able to detect subtle, but important changes in HR in time series. Therefore, several new analysis method of HR behavior, motivated by nonlinear dynamics and chaos theory, have been developed to quantify the dynamics of HR fluctuations [24,25]. In other words, the cardiovascular system is very complex to be of a linear nature, so the only way one can comprehend HRV is by using nonlinear methods as they offer more valid interpretations of ANS activity and is less sensitive to confounders [19].

The Poincaré plot is the most commonly used non-linear method of analyzing HRV. Each data point represents a pair of consecutive beats, the x-axis represents the current NN interval, while the y-axis represents the previous NN interval [19].

Interpretation of HRV

HRV is actually an umbrella term for many different calculations and analysis methods. While there is wide agreement about the interpretation of these measures, there remains some debate about the precise implications of each parameter [26].

Time domain: The SDNN is predominantly indicates sympathetic activity while the RMSSD and pNN50 are indicative of vagal action [13,27].

Frequency domain measures: HF (0.15-0.40 Hz) is considered to reflect the activity of the parasympathetic system (vagus nerve). HF is increased by respiration, cold provocation of the face, and rotation [28]. In the past, LF was thought to reflect sympathetic activity but today, not much is known regarding LF input activity. However, in the scientific community it is now widely accepted that it displays admixture of both divisions of ANS [29]. LF increases during standing, 90° tilt, mental stress, and moderate exercise [14]. LF/HF ratio is considered to show sympathovagal balance [21]. VLF reflects a host of factors: the inputs from chemoreceptors, sympathetic nervous system, thermoreceptors, the renin-angiotensin system and still others [30]. Total power (TP) is a broad measure of autonomic activity. So, for the abnormal cases, this ratio either decreases or increases from the normal range [20,31,32].

Nonlinear method: In Poincare method, the plot is adjusted with an ellipse; three important parameters then define the plot. These are the length of the semi-minor axis of the ellipse SD1, the length of the semi-major axis of the ellipse SD2, and their ratio of SD1 to SD2. The parameter SD1 is the standard of deviation of instantaneous beat-to-beat HRV and it is the measure of short term variability of HR. It is mainly influenced by parasympathetic regulation on the heart. Other parameter SD2 is the measure of long-term variability and is modulated by both parasympathetic and sympathetic nervous system. SD1/SD2 represents the ratio of short term and long-term variability [33].

Software

Methods used to detect heart-beats include: blood pressure, ECG, ballistocardiograms, and the pulse wave signal derived from a photoplethysmograph. Since HRV focuses on the imperceptible changes between each heartbeat (in milliseconds), it is much more complex and requires higher degree of accuracy than heart rate. In addition, it is cumbersome and tedious to study and pinpoint defects in a huge volume of data collected over several hours. Therefore, computer-based tools for in-depth study of data over long intervals have become very useful in diagnostics [34]. Softwares used to analyze HRV, though, not inclusive of all are:

- OleaSense
- Nerveexpress
- Kubios HRV
- Ithlete HRV
- Intellewave
- HRVAS-MATLAB
- HRV Analysis
- Firstbeat sports
- Elite HRV research and personal
- ANSLAB-MATLAB-based program

Acknowledge: Thus, today, HRV measurement is easy to perform, noninvasive, and have good reproducibility, if used under standardized conditions. Softwares are capable of helping investigators to manage artifacts [35,36].

Duration

Classically, it takes ten minutes to get an accurate short-term HRV measure (that consists of 5min of stabilization and next 5min of recording), but today with advancement in research and technology, ultra-short recordings of just one minute are also possible [37].

Position

Ultra-short HRV recordings can be recorded in following positions: supine, seated and standing [14].

Why is HRV Important?

HRV is a tool that indicates both branches of ANS are working especially the parasympathetic branch. Parasympathetic activity decreases the intrinsic heart rate thus provides more space for variability between consecutive heartbeats. Whereas, sympathetic activity accelerates the heart rate and leaves less space for variability

between the successive heart-beats. So, HRV reflects the recovery and readiness of the body [14].

In 1994, Framingham Heart Study detected increased HRV, as the only frequent factor, in all healthy people. So, HRV testing was postulated to serve as a prognostic indicator of aging, fitness levels, all cardiac conditions, chronic disease conditions and stress levels related to job/ work, making complex decisions, public speaking, and performing tests/ exams etc. And also, it is capable to detect autonomic dysfunction as well [14].

So, when the vagal input is active and the sympathetic branch is passive, the heart rate slows down whereas, the HRV becomes higher. This increased HRV signifies an affirmative adaptation or better recovery. As a rule of thumb, it can be said that the higher the person's HRV, the better is the recovery or the fitter the person is and vice versa. For these reasons, lately it has caught the minds of athletes, coaches and the common-men [8].

HRV Analysis in Different Conditions

As aforementioned, HRV is affected by degree of sympathetic and parasympathetic outflow. The activity of the ANS is sensitive to non-modifiable factors like age and gender [38,39] as well as modifiable lifestyle factors like physical activity, smoking, pollution, alcohol consumption [12,40,41], food and water intake [42], circadian rhythm [43,44], heart rate [45,46], blood pressure [47] and several medications [48-50]. Physiological factors such as baroreflex, chemoreflex, thermoregulation, sleep-wake cycle, meals, physical activity, hormones and stress are also found to affect the ANS activity. Lately, peripheral and the central nervous systems are also found to play a major role in affecting the HRV [51]. Thus, even the healthy individuals show haphazard HRV dynamics. While those suffering from diseases show decreased levels of fluctuation.

Respiratory Sinus Arrhythmias (RSA)

Normal resting rhythmicity of the heart is highly variable rather than being monotonously regular. The ECG of a healthy person under resting condition shows periodic variation in RR interval with respiration which is known as RSA. RSA oscillates with the phase of respiration. Cardio-acceleration is observed during inhalation and cardio-deceleration during exhalation. During inspiration, the cardiovascular center constrains the parasympathetic outflow thus quickening the heart rate. Conversely, during exhalation, it reestablishes the parasympathetic outflow resulting in delaying the heart rate by acetylcholine release [52].

Despite many years of investigations, the contribution of the central and peripheral mechanisms together with its functional significance has still remained a subject of considerable debate. Evidences derived from experiments in canines have suggested that the Bainbridge reflex, an autonomous pulmonary reflex, may be involved. Cardiac reflexes and respiratory activities like rib cage movements may also have contributed to RSA [53].

Age, Gender and Circadian Rhythm

It is proved that, HRV depends on age and sex. Bonnemeir et al [54] proved attenuation of RSA with advancing age [55]. Aging also results in loss CNS neurons causing degradation of signal transmission and reduction in regulatory capacity [56]. Henceforth, HRV declines with the aging because of continuous wear and tear [31]. Whereas, regular

physical exercise delays the aging process by increasing HRV by enhancing vagal tone [57-59]. In fetus, HRV increases with gestational age and is high during early postnatal life [60].

It was also found that HRV is usually more in the case of females than men. Hence, compared to men, women are at lower risk of coronary heart disease [61]. There also seemed to be a significant difference in HRV between day and night hours [62].

Physical Activity

Regular physical exercise modifies cardiac autonomic control. Regularly exercising individuals have a disorder that is known as 'athlete bradycardia' and generally have greater HRV compared to sedentary ones [63]. In another study, it was observed that HRV-guided training group could run better than the other group which was pre-planned [64].

In one experiment, intense training period increased HRV but later the variable became stagnant and also decreased subsequently during an overload training phase. However, after a two-week recovery period, HRV bounced back and was even more than the baseline value [65]. Thus, results from multiple studies [66] concludes that HRV distinctively analyze stress that the body undergoes during training and to increase insight into physiological recovery after training. HRV, therefore, is becoming a useful tool for tracking training adaptation or maladaptation of athletes. It also sets an optimal training load leading to improved performances [67]. Thus, the HRV in physical exercise has imparted a significant contribution in sports physiology [8]. Exercise has shown promise, but there is varying efficacy and differences in effect between resistance exercise and aerobic exercise [68].

Sleep

It was proved that during deep sleep HRV decreases in healthy subjects [69]. Compared to stages 2 and 4 Non-REM sleep, the total power is higher in REM sleep and the value slowly increases during each REM cycle [70]. The LF component was higher in REM sleep than in stages 2 and stage 4 Non-REM sleeps. In normal sleep, parasympathetic activity is more around sleep onset and also during sleep stages I, II, III and IV. Conversely, as stated above, the sympatho-vagal balance is reversed during rapid eye movement (REM) sleep [70,71].

The VLF component reflects slow regulatory mechanisms, e.g., the renin-angiotensin system, thermoregulation, is higher in REM sleep than in stage 2 and stage 4 of Non-REM sleep. Again, Gates et al. suggested that, long-lasting alterations existed in autonomic function in snoring subjects [72-74].

The variations in HRV also relates to poor sleep quality as measured by either Pittsburgh Sleep Quality Index or the Epworth Sleepiness Scale) but not with the measures of depression like Beck Depression Inventory and Hamilton Depression Rating Scale. Hence, it can be concluded that insomnia causes adverse changes in autonomic function, irrespective of depression [75].

Infant and Sleep

Investigations in the fetus and newborn have revealed that during REM sleep long-term variability increases whereas, short-term variability decreases compared to Non REM sleep [60,76]. These differences between REM and Non-REM sleep are due to a shift from higher sympathetic tone while REM sleep to a higher vagal tone during

non-REM sleeps [77]. In infants and children, the ratio between LF and HF powers changes with the various sleep stages ($p < 0.02$ in infants; $p < 0.01$ in children): it decreases during deep sleep and increases during REM sleep. Research has found high HF power in children than in infants [78].

SIDS

High-frequency HRV in infants is altered with known risk factors for SIDS including prematurity, prenatal exposures, such as smoking, and environmental exposures, such as prone sleeping [79].

Smoking

HRV analysis Studies have shown that smokers have more sympathetic activity than vagal activity. Also, it was proved in heavy smokers that vagal modulation of the heart is blunted, particularly during a parasympathetic maneuver [80]. Thus, smoking reduces the HRV [80,81]. Recently Zeskind and Gingras have shown that cigarette exposed fetuses have lower HRV and disrupted temporal organization of autonomic control before delivery and postnatal adaptation occur. They also found that possible nicotine withdrawal may have shown the differences in infant neurobehavioral function [82].

Alcohol

HRV decreases in acute alcohol intake. It suggests sympathetic activation together with parasympathetic withdrawal [83]. ECG indices of vagal activity have been reported to have significantly lower indices of cardiac vagal nerve activity than normal volunteers in acute alcoholic subjects [84,85]. In addition, Malpas et al. have shown vagal neuropathy in chronic alcohol dependent men [84].

Infection

HRV has been found to change in illness, and the intensity of this change is prognostic of illness severity. Hence HRV studies may have a role in future diagnosis and management of sepsis along with septic shock [86].

Pontet and colleagues used Fourier spectral analysis as an early marker of MODS in septic patients [87]. In few studies, it is documented that abnormal HRV with decreased variability and temporary decelerations precedes neonatal or infant sepsis. HRV is detected about a day earlier than the clinical diagnosis of sepsis with markers like tachycardia, fever or positive cultures [88,89].

The expected consequence correlates positively with Sequential Organ Failure Assessment (SOFA) score and Acute Physiological and Chronic Health Evaluation (APACHE) II scores [90-93].

Compared with healthy infants, infants who experience sepsis, have similar sample asymmetry in health, and elevated values before sepsis and SIRS ($p = 0.002$) [94].

Blood Pressure

HRV is significantly reduced in patients with left ventricular Hypertrophy (LVH) secondary to hypertension or aortic valve disease. This reduction in baroreflex sensitivity is correlated with cardiac LVH. Hypertensive has decreased baroreflexes and HRV [95].

Myocardial Infarction

A predominance of sympathetic activity and reduction in parasympathetic cardiac control is seen in MI patients [96]. The degree of RSA shows a linear relation with parasympathetic cardiac control and thus can be used as a prognostic tool in patients, who have had a MI. [97,98].

It was shown that, HRV decreases with recent MI [99]. Despite beneficial effects on clinical variables, exercise training, in one study, did not markedly alter HRV indexes in subjects after MI [96].

Two well-known trials, namely the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) and TRAndolapril Cardiac Evaluation (TRACE) demonstrated that decreased HRV is associated with increased mortality after MI [100,101].

Sudden Cardiac Death

Patients of sudden cardiac death have lower HRV compared to healthy individuals [102].

Cardiac Arrhythmia

Sympathetic activity decreases the fibrillation threshold and predisposes to ventricular fibrillation. Vagal activity increases the threshold and appears to protect against malignant ventricular tachyarrhythmias [103].

Congestive Heart Failure (CHF)

HRV is depressed in patients with CHF compared to healthy subjects. Among patients with CHF, HRV is further decreased in patients with more advanced New York Heart Association (NYHA) class, lower ejection fraction and in those with diabetes, hypertension or Ventricular Tachycardia on Holter monitoring [104].

Other Cardiac Diseases

Left Branch Bundle Block, Congestive Heart Block, Sick Sinus Syndrome and Premature Ventricular Contraction [105] on contrary have shown high HRV measures.

Thus, HRV is strongly associated with arrhythmias and all causes of cardiovascular mortality [103,106]. Hence, HRV can detect patients at high risk for future cardiovascular events [107].

Fetal Heart Rate Monitoring

Fetal heart rate monitoring has now become the standard of care during pregnancy/ parturition and has complemented immensely in reducing fetal distress related morbidity [108].

Liver Cirrhosis

Liver cirrhosis decreases HRV. HRV also prognosticates and predicts mortality. Decline in HRV parameters causes rise in plasma pro-inflammatory cytokine levels. It also causes impaired neurocognitive function [109].

Thyroid

Hypothyroidism may result in cardiac autonomic dysfunction. Thus, HRV can be used to monitor cardiovascular-related risk in these patient-populations [110].

Nervous System

Changes in ANS activity have been linked to a variety of mood disorders, including bipolar disorders, depressive disorders, anxiety disorders and schizophrenia [42,111–114]. The significance of HRV analysis in psychiatric disorders arises from the fact that one can easily detect a sympathovagal imbalance (relative cholinergic and adrenergic modulation of HRV) in such pathologies. Also, there are conflicting reports about the HRV and the major depression. It is proved that, in physically healthy depressed adults the HRV does not vary from healthy subjects [115].

Also normal cyclic changes in HR are reduced in the presence of severe brain damage [99,116,117]. Regarding brain damage HRV was less accurate than the Glasgow Coma Scale in predicting outcome. But it was easily accessible and may provide information about the patient's neurologic status [115].

Again, cardiac vagal tone regulation has also been connected to regulation of emotional reactivity, psychological flexibility, social engagement, and reduced prefrontal cortical activity [118–121].

Attention-Deficit Hyperactivity Disorder (ADHD)

Results of study done by Börger N et al. indicated that compared to controls ADHD subjects had a greater 0.10-Hz component which was associated with poor test performance over time. Improvements were demonstrated in a study employing coherence training with a group of middle school students with attention-deficit hyperactivity disorder. Improvements were shown in their short- and long-term memory, ability to focus and behaviors at home and school [122].

Post-Traumatic Stress Disorder (PTSD)

In PTSD subjects, HF component of HRV is lessened whereas the LF component is accentuated. A study among recently returning soldiers from Iraq diagnosed with PTSD found that after relatively brief periods of HRV coherence training showed significant amendments in the capability to self-regulate along with significant improvements in a wide range of cognitive functions were found. It correlated with increased cardiac coherence [123].

Unipolar Depression

Results from several studies show that ANS dysfunction is one of the markers for depression [124]. Reduction in HRV in depressive disorder may be a biomarker of depression [125]. The lower HRV measures in depressed subjects did not change with positive clinical response to either treatment modality. However, these conclusions await for further confirmation [126].

Messerotti Benvenuti et al. found a significant association between somatic symptoms of depression (using the Beck Depression Inventory II) and reduced HRV, measured by SDNN, NN50 and TP (but not RMSSD) [127]. The evidence for parasympathetic deregulation in depressive disorders was critically assessed by Rottenberg in a meta-analysis of 13 cross-sectional studies. He inferred that low mood contributed a small effect size impact upon vagal control, and it only elucidated about 2% variance, with 'medium' effect size (Cohen's $d=0.332$) [128]. Whereas, in another study, Kemp et al. performed a meta-analysis of 18 studies in 673 patients with Major depressive disorder and 407 healthy control subjects. They found that those with depression had lower time-domain HRV, greater 'high-frequency' power measures and greater Valsalva ratios than controls. Non-linear

measures (probably more reliable than linear measures) indicated a negative correlation of depression [10]. It may offer even more specificity for melancholic/somatic subtypes of depressive illness [129] but this requires further confirmation.

Vagal nerve stimulation (VNS) has shown promise as a treatment for severe depressive disorders [130–132]. Whereas, Tricyclic antidepressants decreased HRV, while selective serotonin reuptake inhibitors Mirtazapine and Nefazodone, had no effects on HRV [10].

Bipolar Disorder

Henry et al. found maniacs showed reduction in SDNN. However, the HF score and LF/HF ratio were higher in them. Again, Time-domain measures of HRV, RMSSD and pNN50, were lower in them [133]. In another study, the manic subjects had lower SDNN, RMSSD, TP, LF and HF measures [134]. The SDNN, TP and LF/HF ratios were significantly lower in the bipolar subjects than controls, and HF power was higher, suggesting a reduction in the sympathovagal ratio [135]. There was negative correlation between the CGI-S score and SDNN, RMSSD, pNN50, LF and HF powers. Interpretation was sub-syndromal bipolar depression had reduced HRV [136].

Whereas, after medication, apart from a small decrease in LF/HF ratio with lithium use, there was no notable differences in measures related to mood stabilizer or antipsychotic use. One study showed that HRV measurement could help separation of unipolar with bipolar depression; however it further needs confirmation [137].

Tetraplegia

Tetraplegics have lesion in upper cervical spinal cord. Patients having complete upper cervical cord lesions, however, still have undamaged vagal efferent pathways to the SA node. Despite these, an LF portion is often found in HRV and also there is arterial pressure variability [21].

Cardiac Transplantation

Ramaekers D et al. performed time and frequency domain analysis of Holter recordings in more than hundred heart transplants and four heart-lung transplant recipients. They found HF component evolved overtime attuned with a physiological phenomenon indicating slow vagal reinnervation of the SA [138].

ANS Dysfunction

Increased SNS or diminished PNS activity results in cardio-acceleration. Conversely, a low SNS activity or a high PNS activity causes cardio-deceleration. HRV is a useful signal for understanding the status of the ANS. The normal variability in HR is due to autonomic neural control circulatory system [139]. It is a valuable tool to investigate the sympathetic and parasympathetic function of the ANS. Thus, this should enable protective interpolation at an initial stage when it is beneficial [140].

Diabetes

Diabetes may result in autonomic dysfunction. Traditional measures are able to document the presence of neuropathy, in general only when there are severe symptoms [141]. In studies comparing cardiac autonomic function tests and HRV indices in diabetic patients without abnormal function tests, HRV was lowered [142]. It was again verified

that cardiac (parasympathetic) autonomic activity was diminished in diabetic patients before clinical symptoms of neuropathy become evident [143,144]. The decreased beat-to-beat variability during deep breathing in diabetic neuropathy has also reported [145].

Renal Failure

In chronic renal failure patients, the mean power in the LF band was higher and lower in the HF bands than the corresponding values in the healthy subjects [146].

Metabolic Syndrome

Vagal-mediated HRV indices were reversely linked with many risk factors for Type 2 diabetes namely, insulin resistance, glucose intolerance, hypertension, central obesity and dyslipidemia [147].

Drugs/ Medication Effects in HRV

Beta-Adrenergic Blockade or Stimulation:

Even in those without elevated blood pressure, the beta-adrenergic blocker, atenolol, appears to accentuate vagally mediated rapid oscillations in Heart Rate [148]. Guzzetti et al. [149] studied the effect of atenolol in patients with essential hypertension. They found not only an increase in HF fluctuations, but also a decrease in the sympathetically mediated LF oscillations. This decrease in sympathetic activity was also noticed in postinfarction patients using Metoprolol [150] and in cardiac failure patients using Acebutolol [151]. Thus, beta-blockers are able to restore the sympathetic-parasympathetic balance in cardiovascular disease.

Again, the unexpected observation that prior to MI, beta-blockade enhances HRV only in those animals which are destined to be at low risk of lethal arrhythmias after MI. This can advocate new approaches to post-MI risk stratification [152].

Eryonucu et al [153] explored the effects of β_2 -adrenergic agonist on HRV in asthmatics by using frequency domain measures. The LF and LF/HF ratio were high and TP low at five, ten, fifteen and twenty min after salbutamol and the Terbutaline inhalation. HF, however, did not vary much after those drugs inhalation.

Antiarrhythmic Drugs:

Flecainide and Propafenone but not Amiodarone were documented to lessen time domain of HRV in those with chronic ventricular arrhythmia [154]. Whereas another study showed that Propafenone decreased total HRV and LF greater than HF [155]. Another study with larger sample size established that Flecainide, also Encainide and Moricizine, reduced HRV in post-MI patients but there was no correlation between the HRV and mortality during follow-up [155].

Scopolamine:

Atropine and scopolamine produce a unexpected rise in parasympathetic effects in the heart. HRV varies widely across and within individuals. This, however, indicates that even for parasympathetic activity to the heart, HRV may still be a limited marker [156].

Lithium and Antipsychotics:

Henry et al. found that mood stabilizer or antipsychotic use had no significant effect upon HRV measures [114]. Agelink et al. explored the effects of Amisulpride, Olanzapine, Sertindole and Clozapine on HRV

schizophrenics. They concluded that only clozapine decreased RMSSD, though the variations in all other parameters were very large [157].

Iwamoto et al. measured the effects of Chlorpromazine and Mepromazine in HRV of 211 schizophrenics and 44 controls. They reported that the LF and HF powers were lower, but LF/HF ratios the same in the schizophrenia subjects. This confirmed a decrease in overall autonomic activity without an alteration in sympatho-vagal balance. A negative correlation of antipsychotic dose effect upon LF and HF power were noted. The muscarinic property of Mepromazine and Chlorpromazine may have caused this [158].

Linder et al., in a carefully executed study, measured HRV parameters in 55 young, predominantly female patients (mean age=33 ± 7 years, 67% female) suffering from bipolar disorders (I and II), who were taking antipsychotic medications. Recent use of atypical antipsychotics was linked with a decrease in SDNN and RMSSD and strongly concerned with dopamine receptor 2 affinity (paradoxically, given high affinity in first generation antipsychotics). However, extended use of antipsychotics (up to 5 years) and the use of Lithium or anticholinergic medications were not associated with significantly reduced HRV measures [159].

Antidepressants:

Davidson et al. found that venlafaxine is associated with a greater fall in HRV indices than Paroxetine [160] while Van Zyl et al. found Tricyclic antidepressants are associated with reductions in HRV indices over short recordings (2–40 min) but not long recordings (24 h) [161]. Kemp et al. had found similar HRV trends in Tricyclic antidepressants, while sertraline, mirtazapine and Nefazodone had no measurable effects [162]. Again, Udupa et al., using brief ECG recordings, found time and frequency domains reduced with Tricyclic antidepressants (n=32) and not with SSRIs (n=32).

Agelink et al. demonstrated Reboxetine does not cause any significant changes in vagally mediated HRV indices [163], while Siepmann et al. found that Moclobemide altered measures of HRV. Then, Kemp et al. reported that Escitalopram given to forty-four controls of more than 25 years in age had increased HF component of HRV, both at rest and during psychological stress [164].

Chappell et al. carried out a randomized, controlled, single-blind, cross-over study using a placebo, Duloxetine or Escitalopram. It revealed that time-based and frequency-based HRV measures were not significantly different [165]. Terhardt et al. experimented with Venlafaxine and Mirtazapine. They found that HRV measures declined during treatment with either medication, while heart rate increased [166].

In a meta-analysis of a very large cohort, Kemp et al. found that a large range of antidepressant medications (tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitor and other unspecified antidepressants significantly decreased RMSSD and HF [50].

Benzodiazepines:

Khaspekova et al. found improvement of HRV in a study of Clonazepam in the management of paroxysmal atrial fibrillation. In another study by Komatsu et al. on Midazolam found reduced LF elements of HRV and increased HF elements, during anesthesia [167].

Anticonvulsants:

Lotufo et al., in their meta-analysis, reported less effect of anticonvulsants on HRV [157]. Again, Stefani et al. detected if anticonvulsants was withdrawn, there was no variations in HRV [168].

Thrombolysis:

Thrombolysis affected pNN50 as reported in 95 acute MI patients. HRV was greater after ninety min of thrombolysis [169].

Playing Wind Instruments:

In those playing Native American flutes, it was observed that both low and high-pitched flutes increase HRV [170].

Biofeedback:

HRV biofeedback has shown some positive effects upon HRV [171], Acupuncture has shown encouraging but constraint results, while the benefits from Yoga is largely uncertain [172].

Resonant breathing biofeedback identifies and regulates involuntary HRV. A randomized controlled trial by Sutarto et al. assessed this effect among manufacturing operators having depression and anxiety. They found stress significantly decreased HRV [173].

Therapeutic interventions to enhance HRV:

HRV techniques have been demonstrated to be important in treating cardiovascular diseases, Alzheimer, chronic migraines, leukemia, renal failure, epilepsy, obstructive sleep apnea. Regular endurance exercise tends to increase HRV. Interestingly, HRV is lowered if one is about to get unwell even before the appearance of the symptoms.

Limitation

A number of confounding variables contribute to HRV data collection and interpretation. Designing research methodology to minimize the confounding variables associated is the need of the hour.

Careful attention to the management of confounding variables through more substantial sample sizes, careful subject selection (particularly subjects not taking relevant medications); use of non-linear measures, appropriate statistical analyses would facilitate our knowledge in different conditions.

In HRV, there is no normal range value as in other investigations which can directly point/ throw light about the current health status of the subject. It is based on comparison between a control and a diseased person or same person's before and after conditions. And another thing is one should not compare one's HRV with other human being, since HRV gets influenced by a numerous factor such as hormones, aging overall body physiology, lifestyles etc. Therefore, one should look and compare on one's own HRV along with the direction it is heading for.

Conclusion

HRV offers a relatively simple, well-tolerated and inexpensive method for studying physiological and pathophysiological processes in a noninvasive manner. It is easy to perform, have relatively good reproducibility and provide prognostic information on patients with heart disease. Thus, HRV has prognostic, diagnostic and therapeutic implications.

Attraction towards HRV in scientific community is flourishing every year as technology is growing. Nowadays, many HRV tracking Apps are available which monitor HRV in a daily basis.

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