Review Article

Heart rate variability

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Abstract

Over the last few decades, considerable evolutions were made in the diagnosis of cardiovascular diseases. Interpretive electrocardiography is one of the areas where the progress has been significant. This involves digital recording of cardiac signals at the body surface and subsequent computerized analysis. An important outcome of such analysis is heart rate variability (HRV), which is widely accepted to have prognostic significance in patients with cardiovascular diseases especially after acute myocardial infarction. This is because HRV represents one of the most helpful markers of autonomic balance and hence can predict the tendency to develop fatal arrhythmias.

Recently, interest has grown in relating some diseases to abnormal autonomic nervous system (ANS) activity based on HRV studies, for example: hypertension, bronchial asthma, diabetes mellitus, irritable bowel syndrome, anxiety and so many other diseases. This actually reflects the vital role of the autonomic nervous system in maintaining health.

Unfortunately, HRV is of little practice, if ever, by Sudanese doctors. Therefore, this review is intended to update the physiological basis, determinants, common ways of measurements and some important clinical uses of HRV.

Keywords: Hypertension, bronchial asthma, diabetes mellitus, irritable bowel syndrome, anxiety.

Overall visceral functions of the human body are controlled by the autonomic nervous system through its main two antagonistic branches – the sympathetic and parasympathetic nervous systems. Most of human organs are stimulated by one branch and inhibited by the other. Generally, when the person is in a calm state (relaxation, sleep, etc.), organs such as the heart, lungs, and blood vessels are under the dominance of parasympathetic control. When active (during physical activity, psycho-emotional arousal or stress) these organs are dominated by the sympathetic nervous system. A healthy person is capable of adjusting to external influences by means of quick and adequate sympathetic response. Once that factor disappears, parasympathetic activity increases, which balances overall autonomic activity.

One of the most informative methods of evaluating the balance of the autonomic nervous system, including both branches, is HRV analysis.

Recently, interest has grown in relating some pathology with abnormal autonomic nervous system (ANS) activity based on HRV studies, for example: Coronary heart diseases, hypertension, diabetes mellitus, renal failure, bronchial asthma, irritable bowel syndrome and anxiety[1-14].

HRV measures the time intervals between consecutive heartbeats, which vary under control of the autonomic nervous system. When the parasympathetic system is dominant, the heartbeat intervals (RR intervals) oscillate with higher frequencies. When sympathetic arousal occurs, lower frequency oscillations take place[4,5].

There is a standard mathematical procedure for short-term HRV evaluation, suggested by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[5]. It provides both time and frequency domain analysis of the RR time series.

To perform the HRV analysis, an electrocardiograph (ECG) signal is usually measured. The RR intervals are derived from the ECG as the intervals between consecutive R-wave peaks. The alternative way is to use a photoplethysmograph (pulse wave) – pulse

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wave signal measurement by means of a portable and convenient finger or ear-clip sensor. It emits an infrared (IR) light on the skin. The emitted light is partially consumed by the blood flow. The degree of light consumption / reflection is proportional to the changes in blood flow. The pulse wave signal has periodic peaks that represent blood vessel pulsation. It can be also used to derive the RR intervals (the time between two pulse wave peaks).

Physiology of Heart Rate Variability

Because of continuous changes in the sympathetic-parasympathetic balance, the sinus rhythm exhibits fluctuations around the mean heart rate. Continuous small adjustments in heart rate are made by cardiovascular control mechanisms under steady state conditions. This results in periodic fluctuations in heart rate. The main periodic fluctuations found are respiratory sinus arrhythmia and baroreflex-related and thermoregulation-related heart rate variability[15]. Due to inspiratory inhibition of the vagal tone, the heart rate shows fluctuations with a frequency equal to the respiratory rate[16].

Fluctuation of heart rate originates from self-oscillation in the vasomotor part of the baroreflex loop. These intrinsic oscillations result from the negative feedback in the baroreflex and are accompanied by synchronous fluctuations in blood pressure[17]. The frequency of the fluctuations is determined by the time delay of the system[18,19].

Peripheral vascular resistance exhibits intrinsic oscillations with a low frequency which are influenced by thermal skin stimulation and are thought to arise from thermoregulatory peripheral blood flow adjustments. The fluctuations in peripheral vascular resistance are accompanied by fluctuations with the same frequency in blood pressure and heart rate and are mediated by the sympathetic nervous system[20,21].

Determinants of Heart Rate Variability

Respiratory Frequency

Respiratory sinus arrhythmia increases when respiratory frequency approaches the frequency of the intrinsic baroreflex-related heart rate fluctuations. Respiratory sinus arrhythmia in adults is maximal at a breathing rate of 6 per minute (0.1 Hz). Respiratory rate greater than this frequency, is negatively correlated with the amount of respiratory sinus arrhythmia[22]. Respiratory sinus arrhythmia persists for all exercise intensities and increases during the highest intensities. Its persistence and increase are strongly linked to both the frequency and degree of lung inflation, suggesting a mechanical influence of breathing on respiratory sinus arrhythmia[23].

Blood Pressures

Previous studies have reported decreased HRV among hypertensives[24-26]. Not only hypertension was associated with decreased HRV but also the association between HRV and blood pressure was present across the full blood pressure range[27.28]. Individuals with low HRV at baseline were at an increased risk of developing hypertension over nine years of follow-up, thus indicating that decreased HRV often precedes the development of hypertension[6].

Gender and Age

Studies of gender differences in autonomic regulation demonstrate significantly greater parasympathetic activity in women than do age-matched men [29,30]. However, the results of Umetani et al[31] revealed lower HRV in female compared with male subjects at age less than 30 years old, decreased gender differences at age between 30 – 50 years old and no gender differences at age above 50 years old. Therefore, previous studies examining gender differences in healthy populations report mixed findings possibly due to examining different age groups and a failure to control confounding factors that might affect cardiovascular control.

Body Size

It has been reported that a disordered homeostatic mechanism may promote excessive storage of energy by decreasing sympathetic activity, while defending against weight gain by decreasing parasympathetic activity[32]. In contrast, another study reported that modest diet-induced weight gain elicits

sympathetic neural activation in non-obese males[33]. Masuo et al have reported that plasma norepinephrine concentrations increase following weight gain in men[34]. The results of many studies consistently reveal higher sympathetic activity in obese compared with non-obese individuals[35,36]. However, anthropometric measurements seem to have minor influences on HRV. A task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology suggested comprehensive investigations to obtain formulae of normal values of HRV in large normal populations based on age and gender without special consideration to anthropometry[5]. This is probably justified by the weak correlations between anthropometry and HRV.

Others: HRV measures have been found to be related to several clinical, lifestyle, and laboratory factors e.g. short-term HRV is related inversely to LDL cholesterol and smoking in the population, and directly to alcohol use in women[37]. HRV improves with physical training especially the HF and LF components. These effects must therefore be addressed in investigations on autonomic balance[38].

Heart Rate Variability Measurement

There are different methods of evaluation of the variations in heart rate. Two are the most common and recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[5]:

Time Domain Methods

Frequency Domain Methods

Time domain methods are commonly used for 24-hour data recordings. However, according to the Task force short-term recordings (e.g. 5-min length) can also be analyzed. Frequency domain methods can be easily used for short-term recordings as well. The following heart rate variability parameters are calculated by most HRV machines:

Time Domain Parameters

Calculation of these indices is based on statistical operations on R-R intervals. The main time domain parameters are:

Mean Heart Rate (MHR)

MHR is a mean heart rate value averaged on the entire recording (trial). MHR is measured in beats per minute (BPM).

Mean NN (MNN)

MNN is a mean heart beat interval value averaged on entire recording (NN means normal-to-normal beats). It is used to be called the mean RR interval when it is derived from ECG recording (N-N interval = R-R interval). MNN is measured in milliseconds (ms).

Standard deviation of the NN intervals (SDNN)

SDNN is the square root of variance of N-N intervals. A variance is mathematically equivalent to the total power of spectral analysis, so it reflects all cyclic components of the variability in recorded series of N-N intervals. The actual values of SDNN depend on the length of recording i.e. the longer the recording, the higher the SDNN values are. Thus, in practice it is inappropriate to compare SDNN values derived from the NN recording of different length. SDNN is measured in milliseconds.

Square root of the mean squared differences of successive NN intervals (RMSSD)

RMSSD is an estimate of high-frequency variations in heart rate in short-term NN recordings which reflects an estimate of parasympathetic regulation of the heart. RMSSD is measured in milliseconds.

Frequency Domain Parameters:

Calculation of these indices is based on spectral analysis of R-R intervals. The main advantage of this method is the possibility to study their frequency-specific oscillations. Thus not only the amount of variability but also the oscillation frequency (number of heart rate fluctuations per second) can be obtained. Spectral analysis involves decomposing the series of sequential R-R intervals into a sum of sinusoidal functions of different amplitudes and frequencies by the Fourier transform algorithm. The result can be displayed (power spectrum) with the magnitude of variability as a function of frequency. Thus, the power spectrum reflects the amplitude of the heart rate fluctuations

present at different oscillation frequencies (figure-1). The main time frequency parameters are:

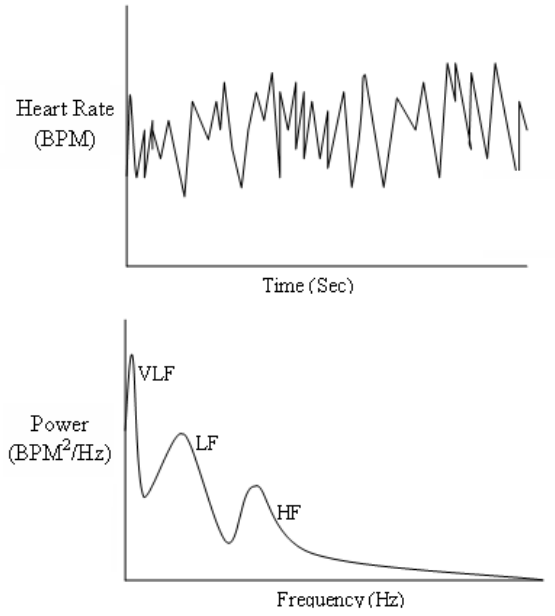

Figure-1: Frequency Domain Heart Rate Variability.

Top. Each point represents the instantaneous heart rate calculated from the R-R interval length. **Bottom.** Heart rate power spectrum of the heart rate trace visualized in the top panel. The three main components (peaks) of the power spectrum correspond to the main periodic fluctuations in heart rate: very-low-frequency (VLF), low-frequency (LF) and high-frequency (HF) fluctuations.

Total Power (TP)

TP is a short-term estimate of the total power of power spectral density in the range of frequencies between 0 and 0.4 Hz. This measure reflects overall autonomic activity. TP is calculated in milliseconds squared (ms^2/Hz).

Very Low Frequency (VLF)

VLF is a band of power spectrum range between 0.0033 and 0.04 Hz. Very Low Frequency band is calculated in milliseconds squared (ms2/Hz). The physiological explanation of the VLF component is much less defined, and the existence of a specific physiological process attributable to these heart period changes might even be questioned. The nonharmonic component, which does not have coherent properties, is commonly accepted as a major constituent of VLF. Thus, VLF assessed from short-term recordings (5 minutes) is a dubious measure and should be avoided when the PSD of short-term ECGs is interpreted.

Low Frequency (LF)

LF is a band of power spectrum range between 0.04 and 0.15 Hz. This measure reflects primarily sympathetic activity. It is a strong indicator of sympathetic activity in long-term recordings. The parasympathetic influences LF when respiration rate is lower than 9 per minute or during taking a deep breath. Thus, when subject is in the state of relaxation with a slow and even breathing, the LF values can be very high indicating increased parasympathetic activity rather than increased sympathetic regulation. It is recommended to maintain a breathing rate not less than 9 breaths per minute during HRV recording to ensure separation of sympathetic and parasympathetic activities. Low Frequency band is calculated in milliseconds squared (ms^2/Hz).

High Frequency (HF)

HF is a band of power spectrum range between 0.15 and 0.4 Hz. This measurement reflects parasympathetic (vagal) activity. HF is also known as a 'respiratory' band because it corresponds to the NN variations caused by respiration; the respiratory sinus arrhythmia (RSA). The heart rate is increased during inhalation and drops during exhalation. Deep and even breathing causes an increase in the amplitude of HF peak on power spectrum. However if respiration rate drops below nine breaths per minute this peak moves into LF frequency range and still represents parasympathetic regulatory activity. High Frequency band is calculated in milliseconds squared (ms^2/Hz).

LF/HF Ratio

LF/HF ratio is the ratio between the power of Low Frequency and High Frequency bands. This measure indicates overall balance between sympathetic and parasympathetic systems. Higher values reflect domination of

the sympathetic system, while lower ones indicate domination of the parasympathetic system. However, when deep and even breathing occurs at rates less than nine breaths per minute, the elevation of this parameter reflects increase of parasympathetic regulation due to the effect of respiratory sinus arrhythmia.

Normalized Low Frequency (LF Norm)

LF Norm is the ratio between absolute value of the Low Frequency and difference between total power and very low frequency. This measure minimizes an effect of changes in very low frequency power and emphasizes changes in sympathetic regulation. Normalized LF is calculated in percentile units.

Normalized High Frequency (HF Norm)

HF Norm is the ratio between absolute value of the High Frequency and difference between total power and very low frequency. This measure minimizes an effect of changes in very low frequency power and emphasizes changes in parasympathetic regulation. Normalized HF is calculated in percentile units.

In conclusion, the representation of LF and HF in normalized units emphasizes the controlled and balanced behavior of the two divisions of the autonomic nervous system. Moreover, the normalization tends to minimize the effect of the changes in total power on the values of LF and HF components. Nevertheless, normalized units should always be quoted with absolute values of the LF and HF power in order to describe completely the distribution of power in spectral components.

Duration and Circumstances of ECG Recording

In HRV research, the duration of recording is dictated by the nature of each investigation. Standardization is needed particularly in studies investigating the physiological and clinical potential of HRV. Frequency domain methods should be preferred to the time domain methods when short-term recordings are investigated. The Task Force of the ESC and NASPE[5] recommends recording time at least 10 times the wavelength of the lower frequency band of the investigated component, and should not be substantially extended so as to ensure the stability of the signal. Thus, recording of approximately 1 minute is needed to assess the HF components of HRV, while approximately two minutes are needed to address the LF component. To standardize different studies investigating short-term HRV, 5-minute recordings of a stationary system are preferred unless the nature of the study dictates another design.

Although the time domain methods, especially the SDNN and RMSSD methods, can be used to investigate recordings of short durations, the frequency methods are usually able to provide results that are more easily interpretable in terms of physiological regulations. In general, the time domain methods are ideal for the analysis of long-term recordings.

A substantial part of the long-term HRV value in cardiac studies is contributed by the day-night differences. Thus, the long-term recording analyzed by the time domain methods should contain at least 18 hours of analyzable ECG data that include the whole night[5].

Little is known about the effects of the environment (type and nature of physical activity and emotional circumstances) during long-term ECG recordings. For some experimental designs, environmental variables should be controlled and in each study, the character of the environment should always be described. The design of investigations also should ensure that the recording environment of individual subjects is similar. In physiological studies comparing HRV in different well-defined groups, the causes of differences between underlying heart rate also should be properly acknowledged.

Clinical Use of HRV

HRV has been the subject of numerous clinical studies investigating a wide spectrum of cardiological and noncardiological diseases and clinical conditions[5]. As will be described below, low HRV has been identified as a strong indicator of risk related to adverse events in healthy individuals and patients with

a large number of diseases, reflecting the fundamental role that autonomic nervous system played in maintaining health[39-44].

Casolo et al study concluded that HRV during the early phase of acute myocardial infarction (AMI) is decreased and is significantly related to clinical and hemodynamic indexes of severity. The causes for the observed changes in HRV during AMI may be reduced vagal and/or increased sympathetic outflow to the heart. It is suggested that early measurements of HRV during AMI may offer important clinical information and contribute to the early risk stratification of patients[39]. Later Rovere et al proved that reduced short-term LF during controlled breathing is a powerful predictor of sudden death in patients with chronic heart failure (CHF) in general. These results refine the identification of patients who may benefit from prophylactic implantation of a cardiac defibrillator[40]. Another predictive value of HRV is that individuals with low HRV at baseline were found to be at an increased risk of developing hypertension over 9 years of follow-up, thus indicating that decreased HRV often precedes the development of hypertension[6].

Several reports have described the relation between epilepsy and cardiac arrhythmias and suggest that changes in autonomic neural control of the heart could be involved in the pathogenesis of sudden unexplained death in patients with epilepsy[41]. Massetani et al evaluate cardiac function in patients with temporal lobe epilepsy. Their findings suggest that the spectral analysis of HRV may detect disorders of autonomic cardiac control in patients with epilepsy, even in the absence of abnormal findings during ECG monitoring. This alteration, which is more severe in cases with right EEG focus, could play a role in the pathogenesis of cardiac arrhythmias[42].

Tükek examined the possible effect of diurnal variability of heart rate on the development of arrhythmias in patients with chronic obstructive pulmonary disease (COPD). They concluded that COPD patients with arrhythmia had circadian HRV disturbances such as unchanged night-time parasympathetic tone and disturbed sympatho-vagal balance in favor of the sympathetic system all day long, which may explain the increased frequency of arrhythmia[43]. On the other hand, the link between nocturnal respiratory disorders and cardiovascular risk consists could be explained by altered sympathovagal balance. This was evident in the results of Spicuzza et al suggested a surge in sympathetic modulation after the obstructive episodes[44].

Regarding researches, many diseases have been extensively investigated by means of HRV studies like bronchial asthma[45-47] and obesity[48-50]. In addition, better understanding of the pathophysiology of many diseases can be achieved by this simple test but remained to be explored by further studies.

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