HEART RATE VARIABILITY – A REVIEW

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Abstract

Heart rate variability (HRV) is a measure of the balance between sympathetic mediators of heart rate that is the effect of epinephrine and norepinephrine released from sympathetic nerve fibres acting on the sino-atrial and atrio-ventricular nodes which increase the rate of cardiac contraction and facilitate conduction at the atrio-ventricular node and parasympathetic mediators of heart rate that is the influence of acetylcholine released by the parasympathetic nerve fibres acting on the sino-atrial and atrio-ventricular nodes leading to a decrease in the heart rate and a slowing of conduction at the atrio-ventricular node. Sympathetic mediators appear to exert their influence over longer time periods and are reflected in the low frequency power(LFP) of the HRV spectrum (between 0.04Hz and 0.15 Hz).Vagal mediators exert their influence more quickly on the heart and principally affect the high frequency power (HFP) of the HRV spectrum (between 0.15Hz and 0.4 Hz). Thus at any point in time the LFP:HFP ratio is a proxy for the sympatho- vagal balance. Thus HRV is a valuable tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. Study of HRV enhance our understanding of physiological phenomenon, the actions of medications and disease mechanisms but large scale prospective studies are needed to determine the sensitivity, specificity and predictive values of heart rate variability regarding death or morbidity in cardiac and non-cardiac patients.

Keywords:Heart rate variability, Sympatho-vagal influences, Measuring methods, Diagnostic marker, Prognostic marker.

INTRODUCTION

Heart rate variability (HRV) is the temporal variation between sequences of consecutive heart beats. On a standard electrocardiogram (ECG), the maximum upwards deflection of a normal QRS complex is at the peak of the R-wave (Figure 1), and the duration between two adjacent R-wave peaks is termed as the R-R interval. The ECG signal requires editing before HRV analysis can be performed, a process requiring the removal of all non sinus-node originating beats. The resulting period between adjacent QRS complexes resulting from sinus node depolarizations is termed the N-N (normal-normal) interval. HRV is the measurement of the variability of the N-N intervals (Reed 2005).

Physiology of Heart Rate Variability

Heart rate variability, that is, the amount of heart rate fluctuations around the mean heart rate (Conny *et al*., 1993) is produced because of the continuous changes in the sympathetic parasympathetic balance that in turn causes the sinus rhythm to exhibit fluctuations around the mean heart rate. Frequent small adjustments in heart rate are made by cardiovascular control mechanisms. 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 (Akselrod *et al*., 1985). Due to inspiratory inhibition of the vagal tone, the heart rate shows fluctuations with a frequency equal to the respiratory rate (Davidson 1976). The inspiratory inhibition is evoked primarily by central irradiation of impulses from the medullary respiratory to the cardiovascular center. In addition peripheral reflexes due to hemodynamic changes and thoracic stretch receptors contribute to respiratory sinus arrhythmia. This is parasympathetically mediated (McCabe 1985). Therefore HRV is a measure of the balance between sympathetic mediators of the heart rate (HR) i.e. the effect of epinephrine and norepinephrine released from sympathetic nerve fibres, acting on the sino-atrial and atrioventricular nodes, which increase the rate of cardiac contraction and facilitate conduction at the atrioventricular node and parasympathetic mediators of HR i.e. the influence of acetylcholine released by the parasympathetic nerve fibres, acting on the sino-atrial and atrioventricular nodes, leading to a decrease in the HR and a slowing of conduction at the atrioventricular node. Sympathetic mediators appears to exert their influence over longer time periods and are reflected in the low frequency power (LFP) of the HRV spectrum (Pomeranz *et al*., 1985). Vagal mediators exert their influence more quickly on the heart and principally affect the high frequency power (HFP) of the HRV spectrum. Thus at any point in time, the LFP:HFP ratio is a proxy for the sympatho-vagal balance.

Frequencies of Heart Rate Variability

In healthy subjects the sinoatrial node located at the posterior wall of the right atrium initiates each beat of the heart. Due to the unstable membrane potential of the myocytes located in this region, action potentials are

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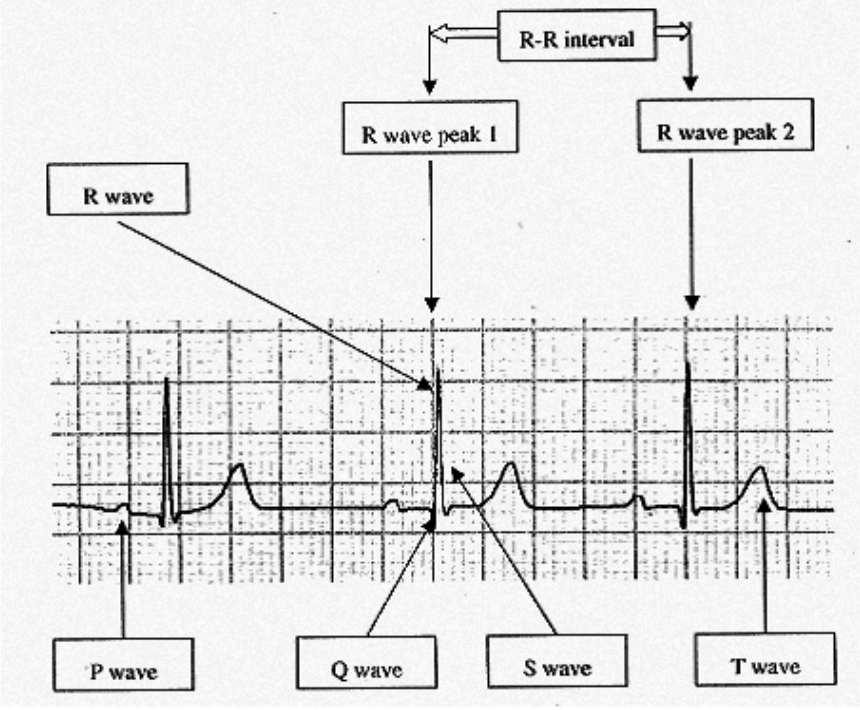

Figure 1: The normal electrocardiogram with component waves labeled (Reed MJ. 2005)

generated periodically at a fairly constant frequency. This relatively constant frequency generated by the auto-rhythmicity of the sinoatrial node is modulated by many factors that add variability to the heart rate signal at different frequencies. These frequencies are classified into (1) ultra low frequencies (ULF; > 5 hrs cycle length) that include the circadian rhythm (Braga *et al*., 2002; Overton 2001; Williams *et al*., 2002) (2) very low frequencies (VLF; > 25 sec cycle length) that are supposed to be affected by temperature regulation (Aoki 2001; Vornanen 2002) and humoral systems (Porter and Rivkees, 2001) (3) low frequencies (LF; > 6 sec cycle length in humans) that are sensitive to changes in cardiac sympathetic and presumably parasympathetic nerve activity (Lanfranchi and Somers, 2002; Malpas, 2002) (4) high frequencies (HF; 2.5 to 6 secs cycle length in humans) that are synchronized to the respiratory rhythm (Barbieri 2002) and are primarily modulated by cardiac parasympathetic inervation (Rentero *et al*., 2002).

A: PHYSIOLOGIC INFLUENCES ON HEART RATE VARIABILITY

1. **Thermoregulation** (Cui 2002; Vollmer and Skott, 2002; Young 2002).
2. **Autonomic nervous System** (Ribbert 1991; VanRavenswaaij *et al*., 1991; Schwartz 1991).
3. **Respiratory Frequency** (Mehlsen *et al*., 1987).
4. **Endocrine Factors** (Scheuer and Bechtold, 2002)**.**
5. **Behavioral State** (Rother *et al*., 1988).
6. **Adenosine** (Gervitz *et al*., 2001).
7. **Heart Rate and Circadian Rhythm** (Furlan *et al*., 1990).

B: PATHOLOGICAL INFLUENCES ON HEART RATE VARIABILITY

1. **Mycocardial Infarction** (Rothschild 1988; Pipilis 1991).
2. **Congestive Cardiac Failure and Coronary Artery Disease** (Sopher *et al*., 1990; VanHoogenhuyze *et al*., 1991).
3. **Heart Transplantation** (Fallen 1988).
4. **Essential Hypertension** (Pagani *et al*., 1984; Guzzetti *et al*., 1988).
5. **Diabetic Autonomic Neuropathy** (Hosking 1978; Ewing 1981; Mackay, 1983).
6. **Neurological Disorders** (Vallbona 1965; Kuroiwa 1983; Heinonen 1985).

C: IATROGENIC INFLUENCES ON HEART RATE VARIABILITY

1. **Atropine** (Ali-Melkkila *et al*., 1991) **and Scopolamine** (Sandrone *et al*., 1994; Cook *et al*., 1991).
2. **β-adrenergic Blockers** (Vybiral *et al*., 1990; LaRovere *et al*., 1994).
3. **Calcium Channel Blockers** (The Multicentre Diltiazem Postinfarction Trial Research Group, 1988).
4. **Antiarrhythmic Drugs** (Lombardi *et al*., 1992; Bigger 1994).
5. **Other Drugs** (Petrie, 1979).

MEASUREMENT OF HEART RATE VARIABILITY

I: TIME DOMAIN METHODS

Time domain methods are considered to be the simplest to perform. In these methods either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous ECG record each QRS complex is detected and the so-called normal to normal (NN) intervals that is all intervals between adjacent QRS-complexes resulting from sinus node depolarizations or the instantaneous heart rate is determined. Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate etc. Thus measurement of HRV first requires the detection of each heart beat. It is usually based on the sequence of RR intervals. This practice neglects the potential presence of fluctuations in PR interval due to modulation of AV nodal conduction. Premature ventricular contractions (PVCs) and premature atrial contractions (PACs) represents additional confounders in assessing autonomic regulation of HR and they should be removed prior to analysis.

(a) **Statistical Methods**

From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods traditionally 24 hours, statistical time domain measurements can be calculated. These may be divided into two classes (1) those derived from direct measurement of the NN intervals or instantaneous heart rate and (2) those derived from the differences between NN intervals. The variables may be derived from analysis of the total ECG recording or may be calculated using smaller segments of the recording period. A straight forward and useful metric of HRV termed the SDNN, is the standard deviation of all normal RR intervals (those measured between conservative sinus beat). The SDNN may be easily calculated from a 24 hour Holtermonitor. In calculating SDNN any RR interval that begins or ends with a PAC or PVC is simply deleted from the sequence. SDNN is typically measured over 24 hours and reported in units of ms. Two variants of the SDNN created by dividing the 24 hour monitoring period into 5 minute segments are the SDNN index and SDANN index (both with units in ms). The SDNN index is the mean of all the 5 minute standard deviations of NN (normal RR) intervals during the 24 hours period i.e. the mean of 288 NN standard deviations while the SDANN index is the standard deviation of all the 5 minute NN interval means i.e. the standard deviation of 288 NN means. These HRV indices mentioned so far are called the time domain measures because they are based on the time series of normal RR intervals. Other time domain indices are the r-MSSD and the pNN50. The r-MSSD (units in ms) or the root-mean-square successive difference, calculates the square root of the mean of the squared differences between successive NN intervals over 24 hours. The pNN50 (percentage units) calculates the percentage of differences between successive NN intervals over 24 hours that are greater than 50 ms. Both of these indices measure short term variation in the NN interval because they are entirely based on comparisons between successive beats. All the HRV indices described above except pNN50 have units of time (ms) and thus strictly speaking are measures of variability in RR interval not HR. HR and RR interval are reciprocals of each other or to be exact. HR =60,000/RR where HR has units of beats per minute (bpm) and RR has units of ms.

(b) **Geometric Methods**

The series of NN intervals also can be converted into a geometric pattern such as the sample density distribution of NN interval durations, sample density distribution of differences between adjacent NN intervals, Lorenz plot of NN or RR intervals. A simple formula is used that judges the variability on the basis of the geometric and/or graphics properties of the resulting pattern. Three general approaches are used in the geometric methods (1) a basic measurement of the geometric pattern for example the width of the distribution histogram at the specified level is converted into the measure of HRV (2) the geometric pattern is interpolated by a mathematically defined shape for example, approximation of the distribution histogram by a triangle or approximation of the differential histogram by an exponential curve and then the parameters of this mathematical shape are used and (3) the geometric shape is classified into several pattern based categories that represent different classes of HRV for example elliptic, linear and triangular shapes of Lorenz plots. Most geometric methods require the RR or NN interval sequence to be measured on or converted to a discrete scale that is not too fine or too coarse and permits the construction of smoothed histograms. The HRV triangular index measurement is the integral of the density distribution. Using a measurement of NN intervals on a discrete scale, the measure is approximated by the value (total number of NN intervals/number of NN intervals in the modal bin) which is dependent on the length of the bin that is on the precision of the discrete scale of measurement. The triangular interpolation of NN interval histogram (TINN) is the baseline width of the distribution measured as a base of a triangle approximating the NN interval distribution (the minimum square difference is used to find such a triangle). Both these measures express overall HRV measured over 24 hours and are more influenced by the lower than by the higher frequencies. The major advantage of the geometric methods lies in their relative insensitivity to the analytical quality of the series of NN intervals (Malik *et al*., 1993). The major disadvantage of the geometric methods is the need for a reasonable number of NN intervals to construct the geometric pattern. In practice recordings of at least 20 minutes but preferably 24 hours should be used to ensure the correct performance of the geometric methods that is

the current geometric methods are inappropriate to assess short term changes in HRV.

II: **FREQUENCY DOMAIN METHODS**

Insight into the nature of HR fluctuations may be gained by analyzing the fluctuations in the frequency domain. The overall power of a star can be determined by measuring the intensity of light emanating from it and by separating this light into component colours with a prism to learn about the composition of chemical reactions within it similarly HRV can be broken into the frequency components that compose the overall variability. Various spectral methods (Kay and Marple, 1981) for the analysis of the tachogram have been applied since the late 1960's. Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency. Methods for the calculation of PSD may be generally classified as nonparametric and parametric. The advantages of the nonparametric methods are (1) the simplicity of the alogorithm used (fast Fourier transform FFT) and (2) the high processing speed. The advantages of parametric methods are (1) smoother spectral components that can be distinguished independent of pre-selected frequency bands (2) easy post processing of the spectrum with an automatic calculation of low and high frequency power components with an easy identification of the central frequency of each component and (3) an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationarity.

(a) **Short Term Recordings**

Three main spectral components are distinguished in a spectrum calculated from short term recordings of 2 to 5 minutes (Pagani *et al*., 1986). VLF, LF and HF components. The distribution of the power and the central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of heart period. The measurement of VLF, LF and HF power components is usually made in absolute values of power (milliseconds squared). LF and HF may also be measured in normalized units which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in normalized units emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system. 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.

(b) **Long Term Recordings**

Spectral analysis also may be used to analyze the sequence of NN intervals of the entire 24 hour period. The result then includes a ULF component, in addition to VLF, LF and HF components. The slope of the 24 hour spectrum also can be assessed on a log-log scale by liner fitting the spectral values. Spectral analysis performed on the entire 24 hour period as well as spectral results obtained from shorter segments i.e. 5 minutes averaged over the entire 24 hour period (the LF and HF results of these two computations are not different) (Berger 1986; Rottman *et al*., 1990) provide averages of the modulations attributable to the LF and HF components.

III: RHYTHM PATTERN ANALYSIS

The time domain and spectral methods share limitations imposed by the irregularity of the RR series. Trends of decreasing or increasing cycle length are in reality not symmetric (Eckberg, 1983), as heart rate accelerations are usually followed by a faster decrease. In spectral results this tends to reduce the peak at the fundamental frequency and to enlarge its basis. This led to the idea of measuring blocks of RR intervals determined by properties of the rhythm and investigating the relationship of such blocks without considering the interval variability. The interval spectrum and spectrum of counts method lead to equivalent results and are well suited to investigate the relationship between HRV and the variability of other physiological measures. The interval splectrum is well adapted to link RR intervals to variables defined on a beat to beat basis (blood pressure). The spectrum of counts is preferable if RR intervals are related to a continuous signal (respiration) or to the occurrence of special events (arrhythmia).

IV: NONLINEAR METHODS

The parameters that have been used to measure nonlinear properties of HRV include I/f scaling of Fourier spectra (Kobayashi and Musha, 1982; Saul 1988), H scaling exponent, coarse Graining spectral analysis (CGSA) (Yamamoto and Hughson, 1991). For data representation, poincar'e sections, low diamension attractor plots, singular value decomposition and attractor trajectories etc. For other quantitative descriptions the D2 correlation dimension, Lyapunor exponents and Kolmogorov entropy have been used (Babloyantz and Destexhe, 1988).

CONCLUSION

The heart rate of healthy persons displays beat-to-beat variations that results from fluctuations in autonomic nervous system activity at the sinus node. Heart rate variability (HRV) decreases under situations of stress either emotional or physical whereas it increases with rest. It is considered a noninvasive marker of autonomic nervous system function (Dekker *et al*., 2000; Hayano 1991) and is used for the diagnosis of diabetic neuropathy. In addition low HRV has prognostic value in patients with myocardial infarction and is associated with risks of cardiac events and sudden deaths (Tsuji *et al*., 1994; Dekker *et al*., 1997; Tsuji *et al*., 1996; Liao *et al*., 1997). Thus HRV is a simple tool that can be used for the diagnosis as well as for the prognosis of many diseases.

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