



Heart Rate Variability: Objective Assessment of Autonomic Nervous System

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ABSTRACT

Heart rate variability (HRV) came into existence by observations of Hon and Lee in 1965 and since then has been a subject of prime importance in medical research. It is derived from changes in RR intervals in a continuous recording of electrocardiogram. Different types of measurements are carried out on these RR intervals in time and frequency domain. Among others, variance, total power, low-frequency (LF) power, high-frequency (HF) power, and LF/HF ratio are frequently used HRV parameters for objective assessment of autonomic function and assessment of several clinical conditions. Poincare plot gives a quick visual impression of HRV. This article describes measurement of all these parameters and their clinical applications.

Keywords: Autonomic nervous system, Diabetic neuropathy, Heart rate variability, Poincare plot, Sympathovagal balance, Total power.

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INTRODUCTION

Autonomic nervous system (ANS) comprises nerves that are involved in the regulation of body involuntary functions. It has two divisions: Sympathetic and parasympathetic. These divisions consist of afferent and efferent

nerves as well as myelinated and nonmyelinated fibers. They both have opposite responses and are complementary to each other. Stimulation of sympathetic nervous system increases heart rate, constricts blood vessels, decreases gastrointestinal motility, and constricts sphincters, whereas increased parasympathetic activity induces opposite effects. Autonomic system supplies both afferent and efferent nerves to the heart. An autonomic nerve has important role in the regulation of the cardiovascular system. Heart can function in the absence of autonomic influences; its rate and force of contraction are altered by autonomic tone. Parasympathetic supply to heart is through the vagus nerves to sinoatrial node, atrioventricular conduction pathways, and myocardium. An efferent vagal nerve slows the heart rate by hyperpolarizing the pacemaker cells and slowing their rate of spontaneous depolarization. A high level of efferent vagal activity produces profound cardiac slowing. Sympathetic supply to heart originates from intermediolateral column of the spinal cord in the upper thoracic region. Sympathetic activity increases heart rate by increasing the rate of depolarization of pacemaker cells. Studies in the past have reported the effect on cardiac output by changes in heart rate, induced by atrial pacing. Cardiac chambers are innervated with afferent fibers from parasympathetic and sympathetic divisions, which help in sensing the extent of filling and pressure generated, thereby helping in their regulation.¹

ASSESSMENT OF ANS

Conventional methods for the assessment of ANS are Valsalva maneuver, slow deep breathing, cold face test, heart rate response to standing, blood pressure response to sustained handgrip, mental arithmetic stress, etc., as described below.

Valsalva Maneuver

Valsalva maneuver test has been most widely used for the assessment of ANS and extensively studied in normal subjects and patients with cardiovascular diseases. It produces transient voluntary elevation of intrathoracic and intraabdominal pressures by straining. The subject blows into a mouthpiece of a manometer to 40 mm Hg for 15 seconds with continuous electrocardiogram (ECG)

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monitoring before, during, and after the procedure. Valsalva ratio is calculated from the ratio of the longest RR interval after strain to the shortest RR interval during strain. A value ≤ 1.2 is considered abnormal.²

Slow Deep Breathing

In this maneuver, the subject breaths at a rate of six breaths per minute. The heart rate is monitored continuously, and the difference between maximum and minimum heart rate is recorded. The data of each breath are recorded and averaged. This test shows parasympathetic vagal activity in humans. A variation in maximum to minimum heart rate of ≤ 10 beats per minute (bpm) is considered abnormal (normal ≥ 15 bpm). Variation of 11 to 14 bpm is considered borderline. The loss of normal respiratory sinus arrhythmia is often suggestive of autonomic neuropathy in diabetes mellitus.²

Cold Face Test (Diving Reflex)

In this test, cold stimulus is applied to face using cold compresses (commercially available gel packs). It causes remarkable increase in the peripheral vascular resistance with a resultant rise in systolic and diastolic blood pressure.³

Heart Rate Response to Standing

In this test, the subject rests in supine for 30 minutes and then acquires standing posture. This results in venous pooling and transient decrease in cardiac output. It is followed with increase in heart rate at around 3 seconds, increasing further to a secondary peak at about 12 seconds and a decline to relative bradycardia at around 20 seconds. The ratio between the highest and lowest heart rate in first 30 seconds from the onset of standing is generally used to quantify the relative bradycardia. A value ≥ 1.04 is considered normal for this test.²

Blood Pressure Response to Sustained Handgrip

In this test, handgrip is maintained at 30% of maximum voluntary contraction for up to 5 minutes by utilizing handgrip dynamometer. The diastolic blood pressure is measured before starting and just before release of handgrip. A difference of ≤ 10 mm Hg is considered abnormal against a control value of ≥ 16 mm Hg. Values ranging between 11 and 15 are considered borderline.²

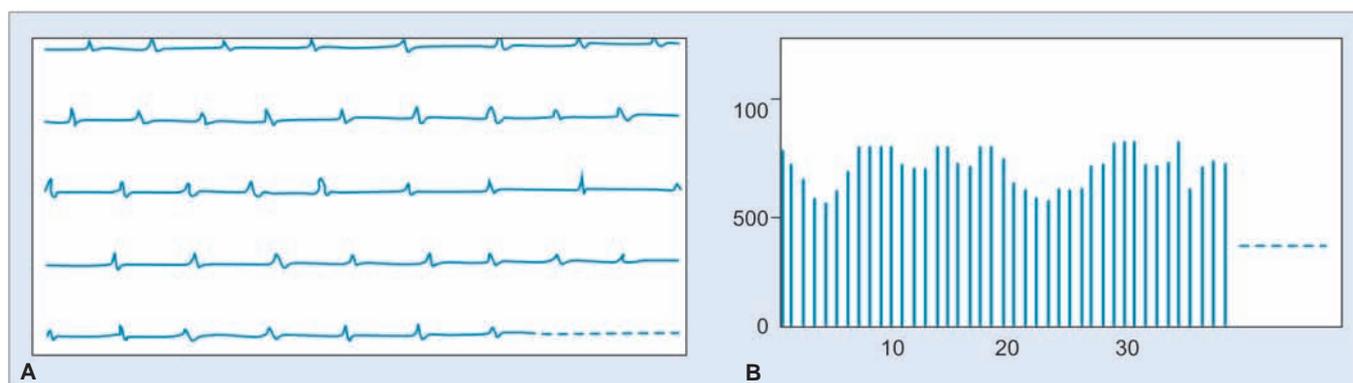
Mental Arithmetic Stress

In this test, the subject is asked to perform serial subtractions, e.g., subtraction of 6 from 100 till reaching the remainder. Skin temperature and heart rate are measured continuously. It has been observed that the skin temperature decreases in normal subjects without neuropathy, but no effect is observed in patients with neuropathy.

The tests described above demand some degree of dexterity on the part of the operator and also cooperation from the patient. There has been a necessity for an objective evaluation of ANS all along. Heart rate variability (HRV) has evolved as an objective tool for the assessment of ANS during the past 50 years, as described in the following section.

HEART RATE VARIABILITY

The average heart rate of a healthy person is around 72 beats per minute. It is, however, never constant. It keeps on changing continuously depending upon the physical and mental state of the subject. A change in heart rate due to increase/decrease in the physical activity of the subject is perfectly understandable and physiological, as the change takes place due to increase/decrease of demand of oxygen and nutrients by the tissues. However, a minor fluctuation in the heart rate is observed even when the subject is physically inactive as shown in (Graphs 1A and B). This is the reason why cardiac activity is not periodic but rhythmic. Study of these fluctuations or variability, even



Graphs 1A and B: (A) Record of QRS pulses in a resting subject. The interval between consecutive pulses is seen to be changing continuously due to HRV; and (B) heart rate value as a vertical line (calculated from interval between two pulses) on the y-axis plotted against beat number. Variations in heart rate are observed to be complex

when the subject is physically inactive, is of immense interest to scientists and physiologists. While investigations have been done for the study of variability in several physiological parameters, majority of investigations are centered on heart rate due to ease of monitoring.

The history of HRV goes back to 1965, when Hon and Lee⁴ observed that diminution of beat to beat variation in the fetal heart rate during labor signified fetal distress and need for a rapid delivery. The clinical importance of HRV became more obvious in the late 1980s, when it was confirmed that HRV was a strong independent predictor of mortality after an acute myocardial infarction⁵ and an objective method for the detection of peripheral diabetic neuropathy.⁶ The following section describes various kinds of measurements of HRV.

MEASUREMENT OF HRV

Time Domain Methods

For analyzing the fluctuations in physiological parameters, time domain measurements are the simplest to start with and to interpret. In order to measure HRV, the QRS complex is detected in a continuous ECG record and the time interval between two consecutive R-peaks arising from sinus node depolarization is called NN interval. Care should be taken to avoid detection of spurious peaks arising due to motion artifact or due to some disease. These NN intervals are used to derive various statistical time domain measures, both for short-term and long-term analysis. In principle, heart rate per minute is the inverse of NN interval value multiplied by 60 (seconds). However, researchers have preferred to use NN interval (or RR interval) directly for variability study and called the same as HRV as it avoids unnecessary computation. As per the Task Force Guidelines,⁷ 5-minute and 24-hour recordings are usually taken for short-term and long-term HRV analysis respectively. Various statistical parameters used for HRV study are as follows.

Mean

The mean, denoted by μ , is the statistician's estimate for the average value of a parameter. It is the sum of all RR interval values divided by the total number of RR intervals, as follows:

$$\mu = \left(\frac{1}{N} \right) \sum_{i=1}^{i=N} RR_i$$

where $RR_1, RR_2, RR_3, \dots, RR_N$ are the observed values of RR intervals during the specified period. The mean is usually used to denote a single value over a period of time.

Standard Deviation of NN Intervals

It is usually denoted by σ and is a measure of variation in the value of NN intervals. A low standard deviation

indicates that the data points tend to be very close to the mean, whereas high standard deviation indicates that the data are spread out over a large range of values. It is obtained as follows:

$$SDNN = \sqrt{\left(\frac{1}{N} \right) \sum_{i=1}^{i=N} (RR_i - \mu)^2}$$

Standard deviation of NN intervals (SDNN) reflects all the cyclic components responsible for variability in the period of recording. When calculated over a long period, it includes both short-term high-frequency (HF) variations and long-term low-frequency (LF) components, seen in a 24-hour period. Normal value of SDNN for 24-hour data is 141 ± 39 ms.⁷ However, for short monitoring period, the LF component diminishes and mainly HF component is seen.

Total Power or Variance

It is the second central moment, i.e., the square of standard deviation. Thus, the variance is a measure of the amount of variation in the values of RR intervals, taking account of all possible values and their probabilities. Variance is mathematically equal to total power of spectral analysis. Thus,

$$\text{Total Power} = \text{Variance} = \left(\frac{1}{N} \right) \sum_{i=1}^{i=N} (RR_i - \mu)^2$$

Standard Deviation of the Average NN Intervals

This parameter is relevant for long-term HRV measurement. In this case, NN interval is determined every 5 minutes and their average is calculated for removal of HF variations. Standard deviation of these average values is called SDANN, which gives an estimate of the changes in heart rate due to rhythms longer than 5 minutes. If $RR^1, RR^2, RR^3, \dots, RR^N$ represent the average RR interval during first 5 minutes, next 5 minutes, and so on, the fluctuations pertaining to frequencies more than 0.0033 are averaged in these values. Standard deviation of these values therefore, represents cyclic variations of frequencies lower than 0.0033 Hz [mainly the ultralow frequency (ULF) band] emerging from circadian rhythm, thermoregulation, etc. A normal value of SDANN for 24-hour data is 127 ± 35 ms.⁷

$$SDANN = \sqrt{\left(\frac{1}{N} \right) \sum_{j=1}^{j=N} (RR^j - \mu)^2}$$

Standard deviation of NN Index

It is more or less complementary to SDANN. Standard deviation value of NN intervals for successive 5 minutes is calculated. This is done over a long period. Mean of these standard deviation values is called SDNN index, since SDNN interval over 5-minute period represents the

cyclic fluctuations of frequency higher than 0.0033 Hz, i.e., mainly the very low frequency (VLF), LF and HF bands. Thus SDNN Index is a measure of VLF, LF, and HF fluctuations.

$$\text{SDNN index} = \left(\frac{1}{N} \right) \sum_{j=1}^{i=N} \text{SDNN}^j$$

where SDNN^j is the SDNN intervals in the j th 5-minute period.

Square Root of the Mean Squared Differences of Successive NN Intervals

Here, firstly the difference between the successive NN intervals is determined and then each value is squared and summed. After this, the mean is calculated and then the square root is taken to obtain the root mean square of successive differences (RMSSD). Thus,

$$\text{RMSSD} = \sqrt{\left(\frac{1}{N} \right) \sum_{i=1}^{i=N} (\text{RR}_{i+1} - \text{RR}_i)^2}$$

Since $\text{RR}_{i+1} - \text{RR}_i$ reflects the HF fluctuations, this parameter is dominated by fluctuations of frequencies greater than 0.2 Hz. Normal value of RMSSD for 24-hour data is 27 ± 12 ms.⁷

NN50 and pNN50

NN50 is the number of interval differences of successive NN intervals greater than 50 ms. This parameter also reflects the HF fluctuations in the RR interval. NN50 divided by the total number of NN intervals is called pNN50.

Frequency Domain Methods

The HRV data collected in time domain may not be interpretable directly as it is a composite signal of large number of inputs. Therefore, it is necessary to analyze the signal in frequency domain. Conversion from time domain to frequency domain is performed most commonly using Fourier transform. This process decomposes the signal into a series of sine and cosine waves with frequencies that are multiples of the fundamental frequency. For time-bound and digitized data, generally discrete Fourier transform (DFT) is used.

In this transform, the sequence of RR interval values (x_n) is transformed into the sequence of N complex numbers X_0, X_{N-1} according to the formula:⁸

$$X_k = \sum_{n=0}^{N-1} x_n e^{-\frac{2\pi i kn}{N}} \quad k = 0, \dots, N-1$$

where "i" represents imaginary unit and $e^{\frac{2\pi i}{N}}$ is the primitive N th root of unity.

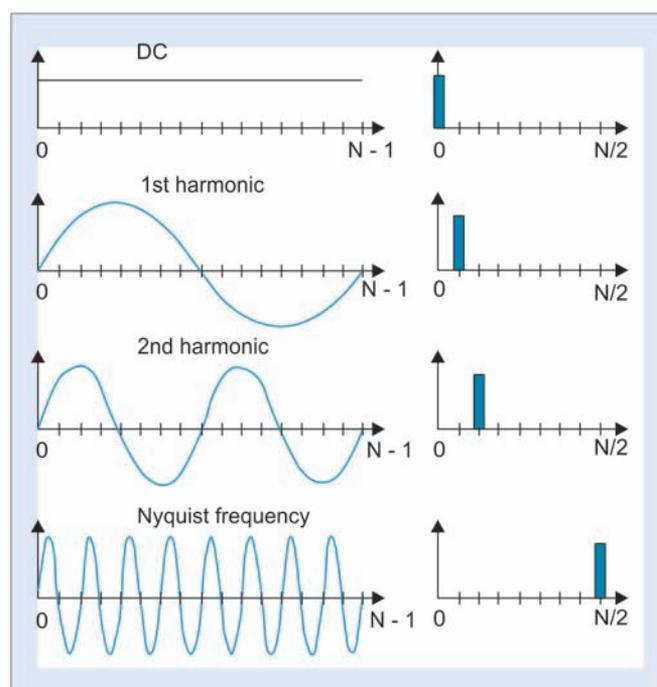
The inverse discrete fourier transform (IDFT) is given by

$$x_n = \frac{1}{N} \sum_{k=0}^{N-1} X_k e^{\frac{2\pi i kn}{N}} \quad n = 0, \dots, N-1$$

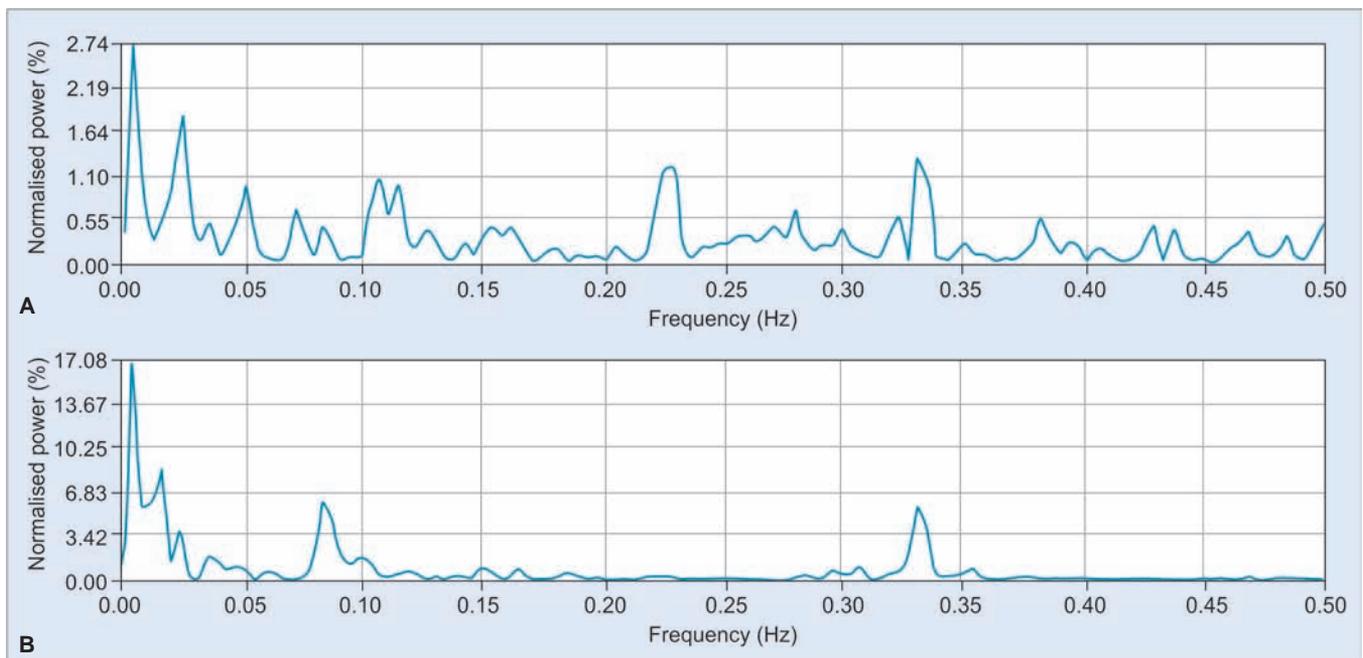
A simple description of these equations is that the complex numbers X_k represent the amplitude and phase of the different sinusoidal components of the input signal x_n . The DFT computes the X_k from the x_n , while the IDFT shows how to compute the x_n as a sum of sinusoidal components. Graph 2 illustrates the DFT of simple sinusoidal signal in time domain.

In a sample size of N , the computations needed for DFT are N^2 . However, they can be reduced to $N \cdot \log_2 N$ if the sample size is an integral exponent of 2. This algorithm is specifically known as fast Fourier transform (FFT).

The above discussion is strictly meant for the periodic signals. Since biological signals are not periodic but rhythmic, for applying FFT onto these signals we have to make them periodic by suitable interpolation techniques. Graphs 3A and B shows power spectral density (PSD) distribution of HRV without and with interpolation respectively. It is clear from the graphs that after interpolation the peaks are distinct and spectrum is less noisy.



Graph 2: Relationship between the input sinusoidal signals of different frequencies and the values of X_k in frequency domain. For instance, if the input values are constant over the entire time period ($N-1$ samples), the value of X_0 (for 0 frequency) is nonzero; when the input values are varying in a sinewave pattern of frequency 1, 2, and 7 Hz, the PSD shows nonzero values of $X_1, X_2,$ and X_7 respectively, revealing that the input signals are sine waves of respective frequencies



Graphs 3A and B: (A) The PSD of HRV without interpolation; and (B) PSD of HRV with interpolation. After interpolation, the peaks are distinct and spectrum is less noisy

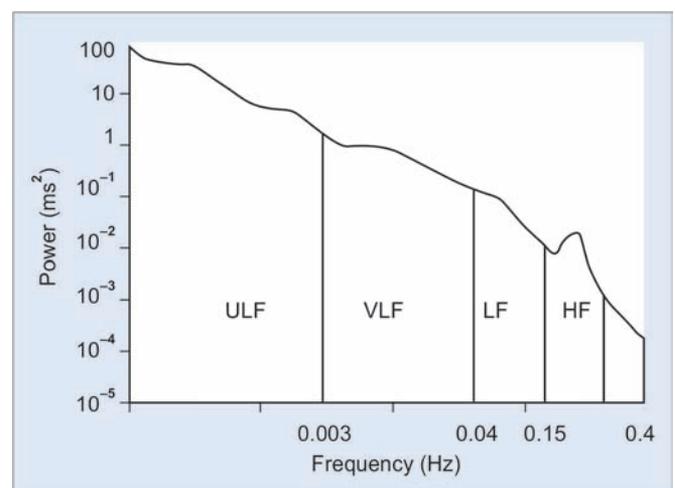
The PSD of interpolated data (5 minutes recording) shows three distinct peaks in the frequency bands of 0 to 0.04 Hz, 0.04 to 0.15 Hz, and 0.15 to 0.4 Hz known as VLF, LF, and HF peaks. Power of VLF, LF, and HF peaks is calculated by integrating the PSD in defined frequency bands. Experimental studies conducted in animals by Sayers,⁹ Akselrod et al,¹⁰ and others have shown that selective blockage of different components of ANS with the help of suitable pharmaceuticals abolishes or dampens some of these peaks. They have identified the frequency regions affected by the sympathetic and parasympathetic nervous system. Conclusive evidence of most of the studies supports the following general consensus¹¹:

- The respiratory rhythm of HRV named as HF spectral component is a marker of vagal modulation.^{12,13}
- The LF spectral component is a marker of sympathetic modulation and corresponds to rhythm of vasomotor waves present in both heart rate and blood pressure variations.^{12,14}
- There exists a reciprocal relation between these two rhythms, which is similar to that characterizing sympathovagal balance.^{12,15}

The PSD for a 24-hour recording is similar to that of Graph 4. It shows large variations in the ULF band and VLF band caused by circadian rhythm, thermoregulation, baroreceptor reflex, and renin–angiotensin system.

Nonlinear Measurements

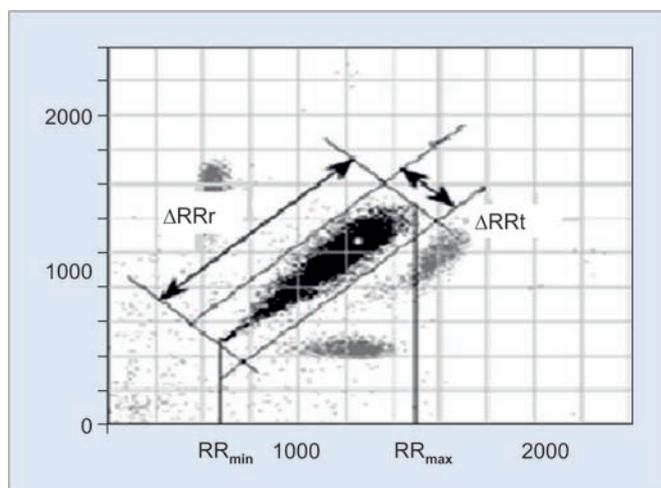
Multiple feedback loops in cardiovascular regulation system make rapid adaptations possible under various physiological and environmental conditions. If such a



Graph 4: Power spectral density (logarithmic scale on both axes) obtained from 24-hour ECG Holter recording. Only the LF and HF components show discernible peaks in the spectrum; VLF and ULF can be approximated by a line in this plot

system is analyzed for heart rate and blood pressure time series, we lose a lot of information on the dynamic patterns. These dynamic patterns are used by the cardiovascular regulation system to adjust heart rate and blood pressure. Therefore, nonlinear methods of signal analysis can be more useful when characterizing complex dynamics. The idea of using nonlinear statistics in the analysis of heart rate and blood pressure time series data is theoretically very sound.

In Poincare plots, the length of each RR interval (RR_{i+1}) is plotted against the preceding RR intervals (RR_i). Poincare plots might be seen as an easy and an informative method for visual presentation of HRV



Graph 5: Poincare plot (length of each RR interval RR_{i+1} is plotted against the preceding RR intervals RR_i) with estimation of different parameters based on the plot. ΔRR_r , difference on plot diagonal between minimal (RR_{min}) and maximal (RR_{max}) RR values, i.e., major axis diameter of ellipse represents amplitude of the variation; ΔRR_t , minor axis diameter of ellipse represents the frequency of variation; area inside the ellipse P represents overall HR variability

and assessment of autonomic control. Graph 5 shows various parameters and their measurements using Poincare plot.

ΔRR_t can be correlated with the frequency of variability. For example, Graph 6 shows Poincare plot for sinusoidal signal of frequencies 1/6, 1/12, and 1/60 Hz. As

can be seen from the graph, ΔRR_t is highest for frequency of 1/6 and lowest for frequency of 1/60 Hz.

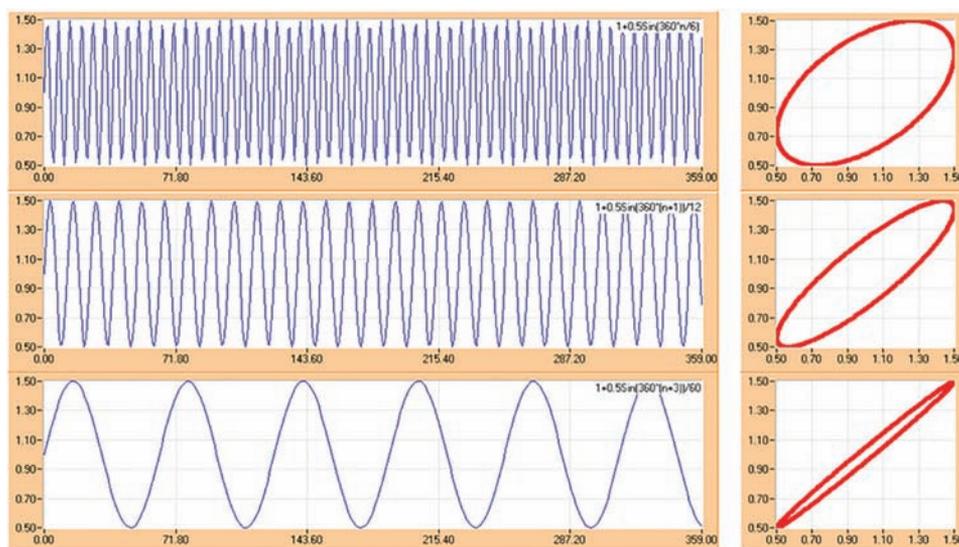
Poincare plot is classified into several categories according to their shapes. Fan shape pattern is considered to represent normal heart rate dynamics, whereas "Torpedo shape," "Complex shape," or "Narrow shape" patterns indicate abnormal heart rate dynamics in various conditions.

CLINICAL APPLICATIONS OF HRV

Early Detection of Peripheral Neuropathy

Bianchi et al⁶ have conducted a study on 14 normal subjects and 40 diabetic patients, including 21 having associated autonomic neuropathy. They have measured powers of HF and LF components together with their ratio (LF/HF), which were considered to provide quantitative indices of the sympathovagal dynamic balance in the control of heart rate. Their observations are summarized in Table 1.

As can be seen from Table 1, total power as well as HF power is drastically decreased in neuropathic diabetics (ND). Also, the behavior of HF power on standing and during controlled respiration (CR) is different than that of normals and nonneuropathic diabetics (NND). The LF/HF is significantly elevated in resting position and its increase on standing is minimal in ND group as compared with control and NND groups. These observations suggest



Graph 6: Examples of Poincare plots arranged from maximum (top) to minimum (bottom) frequency of the input signal. Note that as frequency of the input signal is decreased, the width of ΔRR_t is also decreased

Table 1: Heart rate variability observations in controls and diabetic patients

Sl. no.	Subjects	Total power (ms^2)			HF power (ms^2)			LF/HF ratio		
		Resting	Standing	CR	Resting	Standing	CR	Resting	Standing	CR
1	Control	2,600	2,100	2,400	1,350	250	1300	2	16	6
2	NND	2,500	1,300	2,200	1,250	400	1000	1	8	3
3	ND	300	400	400	50	75	150	4.5	5	2.5

Table 2: Total power values in controls and cardiac transplant recipient patients

Sl. no.	Subjects	No. of subjects	Log of total power
1	Controls	6	0.982 ± 0.206
2	Cardiac transplant recipients	84	-0.766 ± 0.541
3	Cardiac transplant recipients (no rejection)	18	-0.909 ± 0.577
4	Cardiac transplant recipients (rejection)	34	-0.602 ± 0.525

that HRV can be used to objectively assess autonomic neuropathy in diabetic subjects.

Patient Monitoring

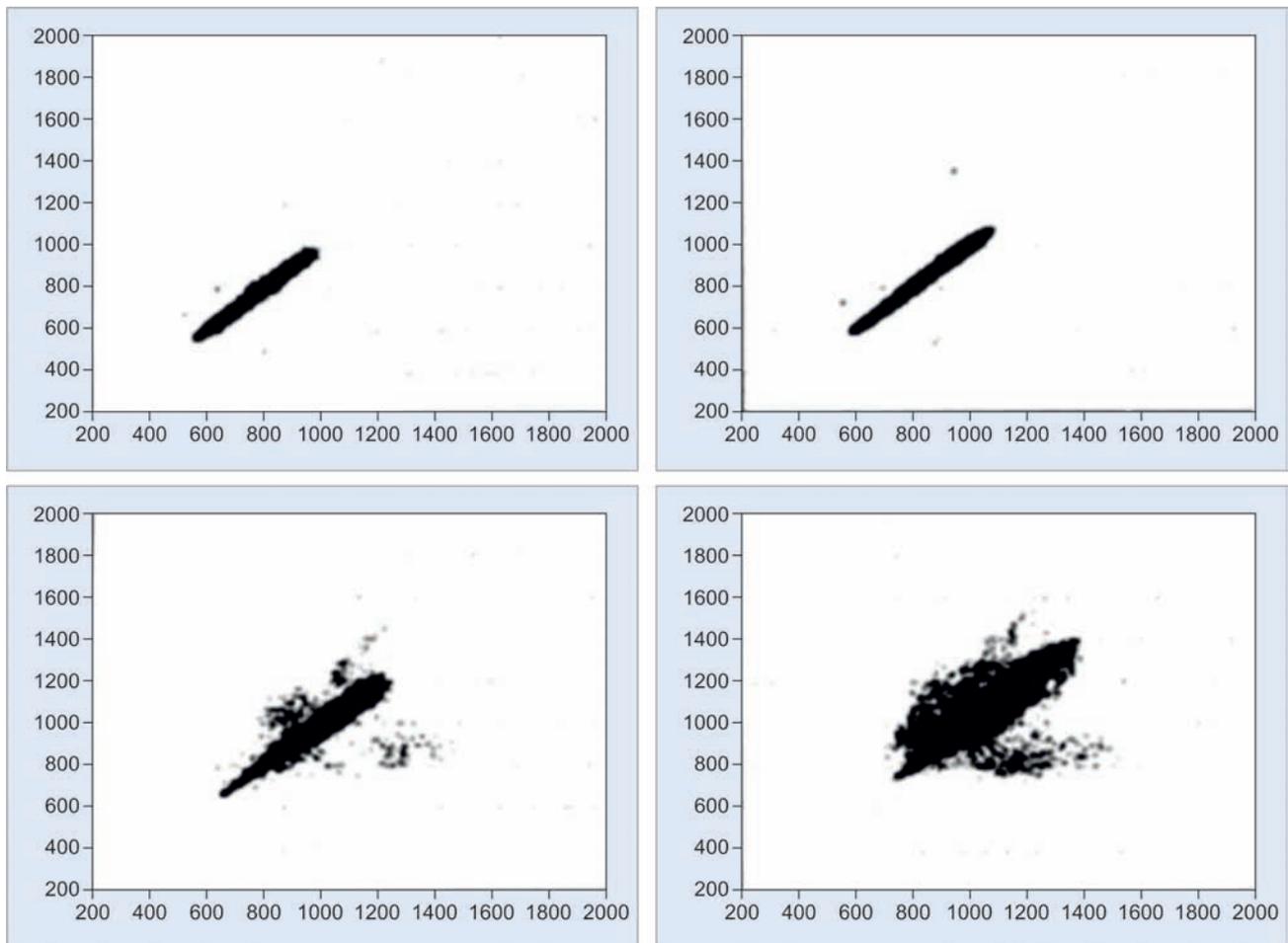
The HRV has proved to be of great value in intensive care monitoring. It is possible for the doctor to see HRV on 24-hour basis and discern the positive and negative epochs and relate them with the treatment/clinical condition of the patient. Increase in HF power has to be considered a sign of good prognosis in patients with acute myocardial infarction. Sands et al¹⁶ have reported a study in 6 control subjects and 84 cardiac transplant recipient patients. Their observations in logarithm value of total power are given in Table 2.

As can be seen from the table, total power is drastically reduced in cardiac transplant recipient patients. It

can also be seen that there is significant increase in HRV in transplant recipients who have shown rejection as confirmed by biopsy within 48 hours of the recording of HRV. Thames et al¹⁷ have reported the regrowth of parasympathetic innervation of the heart after cardiac transplantation in dogs. Also the enervated dogs developed respiratory sinus arrhythmia within 3 to 24 months postoperatively. Similar observation is reported by Hrushesky et al¹⁸ in human beings.

Drug Response

Poincare plot reflects dynamic changes and is very useful for quick assessment of drug response. Copie et al¹⁹ have observed marked changes by administration of bisoprolol in Poincare plot (bottom graph in Graph 7) in contrast to placebo (top graph in Graph 7).



Graph 7: Effect of bisoprolol on HRV in patients with heart failure. Scatter plot evolution in a patient who received placebo (top) and a patient who received bisoprolol (bottom) (Courtesy: Copie et al¹⁹)

CONCLUSION

Measurement of HRV in human subjects does not require high degree of expertise unlike conventional methods like Valsalva maneuver, slow deep breathing, etc. Therefore, it is the method of choice for the objective assessment of autonomic function. In view of its clinical applications, HRV is the method of choice in intensive care mentoring to assess the therapeutic response of the patient. Also, HRV is very useful in the detection of peripheral neuropathy in diabetic subjects.

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