Heart Rate Variability: Measurement and Clinical Utility

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Electrocardiographic RR intervals fluctuate cyclically, modulated by ventilation, baroreflexes, and other genetic and environmental factors that are mediated through the autonomic nervous system. Short term electrocardiographic recordings (5 to 15 minutes), made under controlled conditions, e.g., lying supine or standing or tilted upright can elucidate physiologic, pharmacologic, or pathologic changes in autonomic nervous system function. Long-term, usually 24-hour recordings, can be used to assess autonomic nervous responses during normal daily activities in health, disease, and in response to therapeutic interventions, e.g., exercise or drugs. RR interval variability is useful for assessing risk of cardiovascular death or arrhythmic events, especially when combined with other tests, e.g., left ventricular ejection fraction or ventricular arrhythmias. **A.N.E. 2005;10(1):88–101**

autonomic nervous system

Heart rate responds dynamically to physiologic perturbations mediated by the autonomic nervous system via efferent vagal and sympathetic nerve impulses.[1,2] Even at rest heart rate fluctuates cyclically. High frequency (HF) cyclic fluctuations are modulated by ventilation, mediated entirely by changes in vagal outflow.[3–7] Slower fluctuations occur due to baroreflexes or due to thermoregulation.[3–7] The greatest variation of heart rate occurs with circadian changes, particularly the difference between night and day heart rate, mediated by complex and poorly understood neurohormonal rhythms.[6,8] Exercise and emotion also have profound effects on heart rate. Fluctuations in heart rate reflect autonomic modulation and have prognostic significance in pathological states.[9–45]

There are two common settings in which heart rate variability (HRV) is measured. First, HRV is assessed under controlled laboratory conditions with short-term measurements before and after tilt, drugs, controlled ventilation, or other maneuvers selected to challenge the autonomic system. Secondly, HRV can be determined from 24-hour electrocardiographic (ECG) recordings made while subjects perform their usual daily activities. Twenty-four-hour ECG recordings are particularly useful for risk stratification in a variety of pathological entities, but can also be useful for quantifying autonomic dysfunction.[5,12,16,46–52]

Methods for quantifying HRV are categorized as: time domain, spectral or frequency domain, geometric, and nonlinear. Baroreflex sensitivity (BRS) and heart rate turbulence can also be considered measures of HRV. A short discussion of each will follow.

TIME DOMAIN MEASURES OF HEART RATE VARIABILITY

In time domain analysis, the intervals between adjacent normal R waves (NN intervals) are measured over the period of recording.[53] A variety of statistical variables can be calculated from the intervals directly and others can be derived from the differences between intervals (Table 1).[53–55]

SDNN, the standard deviation of all normal RR (NN) intervals during a 24-hour period, is the most commonly used time domain measure of HRV. A major component of SDNN magnitude (approximately 30–40%) is attributable to day:night difference in NN intervals. Accurate calculation of SDNN requires careful editing to exclude ectopic beats, artifact, and missed beats. Artificially short or long intervals occurring as a result of these events can artificially increase SDNN. Most laboratories require at least 18 hours of usable data to calculate SDNN in a 24-hour recording.

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Table 1. Time Domain Measures of HRV Calculated over 24 Hours

SDNN	Standard deviation of all normal to normal R-R (NN) intervals
SDANN	Standard deviation of 5-minute average NN intervals
ASDNN (index)	Mean of the standard deviations of all NN intervals for all 5-minute segments in 24 hours
rMSSD	Square root of the mean of the squares of successive NN interval differences
NN50	The number of NN intervals differing by >50 ms from the preceding interval
pNN50	The percentage of intervals >50 ms different from preceding interval
Night-day difference	Mean night R-R interval minus mean day R-R interval

SDANN, the standard deviation of the 5-minute average NN intervals, provides a "smoothed out" version of SDNN, i.e., measures long-term fluctuations.[12] SDANN is less subject to editing error than SDNN because averaging several hundred NN intervals minimizes the effects of unedited artifacts, missed beats, and ectopic complexity. As such, SDANN is also much less affected by abnormal rhythms and may even permit risk stratification in atrial fibrillation.

ASDNN (or SDNN index) is the average of the 5-minute standard deviations of NN intervals.[53] It reflects the average of changes in NN intervals that occur within 5-minute periods. ASDNN is significantly correlated with both SDNN and SDANN, because low and high HRV tend to be global phenomena, decreasing or increasing all measures.

The most common variables calculated as differences between normal R-R intervals are rMSSD, NN50, and pNN50.[56,57] rMSSD is the square root of the squares of the successive differences between NN intervals, essentially the average change in interval between beats.[58] NN50 is the absolute count of differences between successive intervals >50 ms,[17] and pNN50 is the proportion of differences >50 ms.[12] In the presence of normal sinus rhythm and normal AV-nodal function, each of these measures quantifies parasympathetic modulation of normal R-R intervals driven by ventilation.

All other time domain measures are variants of those discussed above and correlate highly with one or more of the previously discussed measures.

SPECTRAL ANALYSIS OF R-R INTERVALS

Either fast Fourier transformation or autoregression techniques can be used to quantify cyclic fluctuations of R-R intervals.[59] Traditionally, spectral analysis has been done in short-term laboratory studies; often standard 5-minute ECG segments are analyzed. Two peaks are seen in 5-minute R-R interval power spectra, a HF peak between 0.15 and 0.40 Hz and a low frequency (LF) peak between 0.04 and 0.15 Hz (Fig. 1, upper panel).

High frequency power reflects ventilatory modulation of R-R intervals (respiratory sinus arrhythmia) with the efferent impulses on the cardiac vagus nerves, and is abolished by atropine. When the frequency of ventilation is changed, the center frequency of the HF peak moves with the ventilatory rate.[60,61] The amplitude of the peak, reflecting the degree to which R-R intervals are affected by ventilation, is similar over normal ventilatory frequencies[60,61]

Low frequency power is modulated by baroreflexes with a combination of sympathetic and parasympathetic efferent nerve traffic to the sinoatrial node.[1,3,6,37,63,64] Standing or head up tilt typically causes a modest increase in LF power and a substantial decrease in HF power.[63] Atropine almost abolishes the LF peak, and beta blockade prevents the increase caused by standing up. Various manipulations of high and LF power, e.g., normalization or the LF/HF ratio has been applied in an attempt to better estimate sympathetic activity. These manipulations are based on a somewhat simplistic "ying-yang" model of cardiac autonomic function. Results have been illuminating under some circumstances (e.g., tilt table testing) and readily misinterpreted under others (numerous papers in which increases in the LF/HF ratio due to reductions in HF power have been interpreted as increased sympathetic activity).

R-R interval power spectra also have been computed using data from 24-hour ECG recordings and categorized into total power and four mutually exclusive power bands, ultra low, very low, low, and HF power (Fig. 1, lower panel).[9,10] Total and ultra-low frequency power are best calculated from a R-R interval periodogram of the entire 24-hour recording. Instead of computing the 24-hour power spectrum, spectral analysis often is performed on

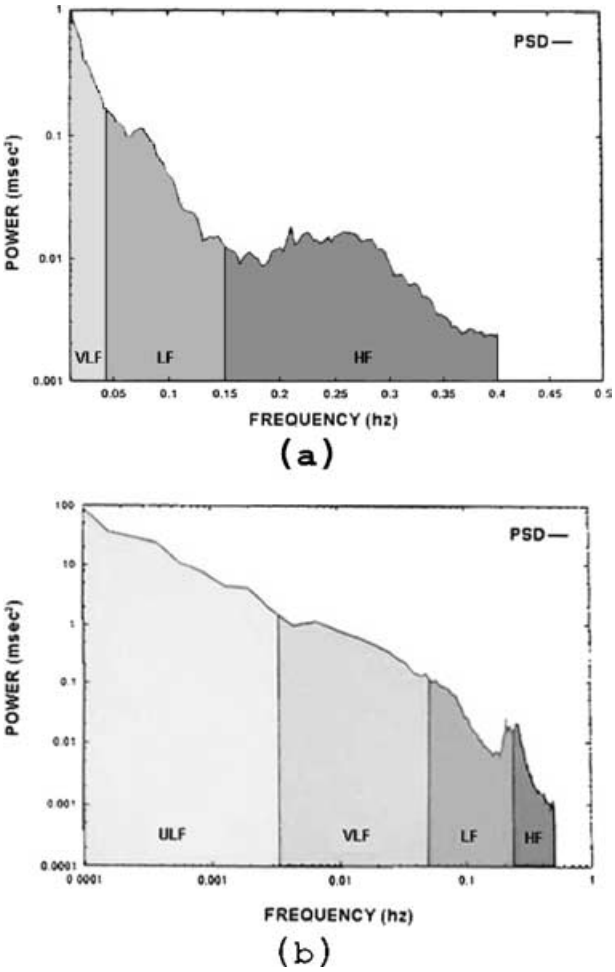

Figure 1. R-R interval power spectra. The upper panel plots log power versus frequency for a 5-minute periodogram and the lower panel plots log power versus frequency for a 24-hour periodogram. In the lower panel, frequency is plotted on a log scale and the Y axis is markedly compressed compared with the upper panel. Note the exponential increase in power as frequency decreases below the low frequency band for both graphs. The two graphs resemble each other, but with much greater amplitude in the 24-hour plot (lower panel). The similarity in the graphs is consistent with fractal behavior for power below the low frequency band.

5-minute segments from 24-hour recordings. HF and LF power are calculated for each suitable segment and then averaged. Either method is suitable for estimating the average 24-hour HF and LF power. Unfortunately, commercial Holter systems sometimes calculate total power in each 5-minute segment and report its average value over 24 hours. Because the 5-minute value does not measure fluctuations in R-R intervals with cycles longer than 5 minutes, such as those due to day:night differences, the 5-minute value is much smaller than total 24-hour power. The large difference between 5-minute and 24-hour total power can cause confusion; it is the 24-hour value that is more useful for prognosis (read below).

Most of the power of HRV in a 24-hour recording resides in the frequencies below HF and LF power which together account for <10% of the total power over 24 hour. About 12% of power is accounted for by fluctuations in R-R intervals that have a period between 20 seconds and 5 minutes (0.0033–0.04 Hz).[10] This spectral band is called very low frequency (VLF) power. The exact physiologic mechanism responsible for VLF is a matter of dispute, but, like most other forms of HRV, VLF power is abolished by atropine, suggesting that it uses a parasympathetic efferent limb.[64,65] Very low frequency power is also reduced by about 20% by ACE inhibition, suggesting that, at least in part, it reflects the activity of the renin-aldosterone system.[66,67] Others have suggested that VLF power reflects thermoregulation or vasomotor activity.[68] Bernardi et al. showed that physical activity can exert a large effect on VLF power.[69] In addition, sleep-disordered breathing can cause exaggerated values for VLF power, seen as clear peaks on plots of the HRV power spectrum during the night.[70]

The lowest frequency band in the 24-hour R-R interval power spectrum is ultra low frequency (ULF) power, which quantifies fluctuations in R-R intervals with periods between every 5 minutes and once per 24 hours (ULF <0.003 Hz). Ultra low frequency power is strongly associated with SDANN.[11]

Although the physiologic basis for ULF and VLF power are far less clear than HF and LF power, they have proven to be more powerful risk predictors in cardiovascular diseases.[10] It is important to point out that accurate editing, and attention to the uniformity of beat onset detection, is crucial for 24-hour spectral analysis. Including nonNN intervals in the R-R interval time series will substantially degrade spectral analysis, even more so than for time domain analysis. Each of the 24-hour spectral measures has an equivalent time domain variable, which is highly correlated with it (Table 2) because both are influenced by the same physiologic inputs and because of mathematical relationships.[11] For example, SDNN is the square root of the total variance in normal R-R intervals, whereas total power is equivalent to total variance. In practice, the

Table 2. Highly Correlated Time and Spectral Measures of HRV

Time Domain	Frequency Domain
SDNN	Total power
SDANN	ULF power
ASDNN	VLF power
PNN50, rMSSD	HF power
Highly Correlated Time Domain Measures	
SDNN	SDANN
RMSSD	pNN50

correlations between TP and SDNN, ULF power and SDANN, VLF power, and SDNN index exceed 0.85 and the correlations between ULF power (approximately 80% of the total power) and TP, SDNN, SDANN also exceed 0.8. Use of time domain variables, e.g., SDNN and SDANN rather than the spectral measures for a particular study is a matter of preference and capability. Because all frequency domain and some time domain HRV variables have skewed distributions, the data are usually log transformed for parametric statistical analyses.

GEOMETRIC MEASURES OF R-R INTERVALS

Heart rate variability triangular index, a geometric measure of HRV, has been used extensively by investigators at St. George's Hospital in London.[19,37,54] Bedeviled by difficulties in efficiently dealing with ectopic complexes, missed beats, and noise in analyzing recordings, they created histograms of the intervals by sorting them into 7.8 ms bins. They then fitted a triangle, using a least squares technique, to the height of each interval. Two measurements were made, the baseline width of the triangle in milliseconds and the ratio of the total number of beats divided by the number of beats in the modal bin. The latter quantity is called HRV triangular index or just HRV index, and is essentially the area of the triangle divided by the area of the modal bin. The calculation of HRV index minimizes the influence of outlier R-R intervals, i.e., those much longer or shorter than the usual, thereby substantially reducing the influence of missed beats, artifact and ectopic complexes. With accurate editing, HRV index and SDNN are strongly correlated and both are powerful risk stratifiers after myocardial infarction.[19,37,54]

NONLINEAR MEASURES OF R-R INTERVAL FLUCTUATIONS

Although time and frequency domain measures of HRV quantify HRV on various time scales, nonlinear HRV measures attempt to quantify the structure or complexity of the R-R interval time series. For example, a random series of R-R intervals, a normal series of R-R intervals and a totally periodic series of R-R intervals might have the exact same SDNN, but their underlying "organization" would be completely different. A large number of nonlinear measures of HRV have been studied, but only a few have shown clear utility in risk stratification (Fig. 2). These include the power law slope, the short- and long-term fractal-scaling exponent, and SD12, a measure derived from Poincare plots.

Power Law Slope

In normal sinus rhythm, spectral power, measured over 24 hours, shows a progressive, exponential increase in amplitude with decreasing frequency.[71] (Fig. 1b) This relationship can also be plotted as the log of power (Y axis) versus the log of frequency (X axis), which transforms the exponential curve to a line whose slope can be estimated (Fig. 2, bottom panel). In a log-log plot, the power law slope between 10^{-2} and 10^{-4} Hz is linear with a negative slope, and reflects the degree to which the structure of the R-R interval time series is self-similar over a scale of minutes to hours. Decreased power law slope has been shown to be a marker for increased risk of mortality after myocardial infarction.[72]

Detrended Fractal Scaling Exponent

This measure, also referred to as α_1, is computed from detrended fluctuation analysis (DFA) and is a measure of the degree to which the R-R interval pattern is random at one extreme, or correlated at the other on a scale of 3–11 beats (Fig. 2, middle panel).[73] A totally random R-R interval pattern has a value for α_1 of 0.5, whereas a totally correlated pattern of R-R intervals, i.e., one that is totally periodic, has a value of 1.5. α_1 is usually repeatedly measured within a period of 1000 R-R intervals and then averaged. Normal values are about 1.05. Decreased values for α_1 are strong predictors of outcome after MI.[73,74] Another measure, α_2 (or DFA2) can be computed in a similar way on a scale of

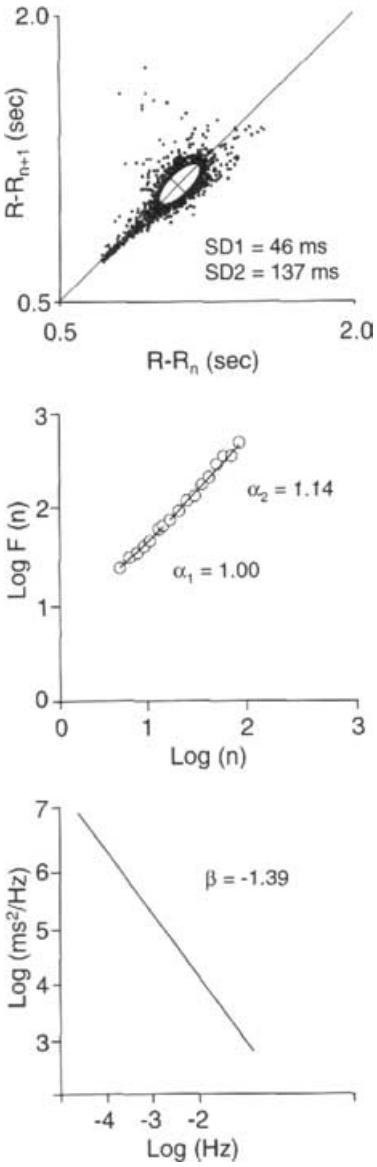

Figure 2. Nonlinear Measures of R-R Interval fluctuations. The top panel shows a two-dimensional vector analysis of a Poincaré plot; the middle panel shows calculation of detrended fluctuation analysis (DFA); and the bottom panel shows calculation of the power law slope. The Poincaré plots and DFA analyses are derived from a 1-hour recording at night in a healthy subject. The power law slope is derived from a 24-hour recording. Abbreviations: SD1, short-term beat-to-beat R-R variability from the Poincaré plot (width); SD2, long-term beat-to-beat variability from the Poincaré plot (length); α_1, the short-term fractal scaling exponent for 4–11 beats; α_2, the intermediate-term fractal scaling exponent (11–20 beats), β, power law slope (adapted from Ref.73)

12–20 R-R intervals. α_2, however, has not proved to be especially useful in risk stratification.

The Poincaré Plot

The Poincaré graph plots each R-R interval as a function of the next R-R interval (Fig. 2, top panel) and provides an excellent way to visualize patterns of R-R intervals.[73] Usually, the R-R interval time series is plotted for an entire 24 hours, but plots of shorter periods, e.g., hourly, can reveal details obscured in a 24-hour plot that involves about 100,000 points. Poincaré plots that reveal abnormal R-R interval patterns have been characterized as "complex." In addition, Poincaré plots that reflect extremely low HRV have also been classified as abnormal. SD12 is determined by fitting an ellipse to the Poincaré plot. SD1 is the short axis of this ellipse and SD2 is the long axis. SD12 is their ratio. As the plot becomes more complex, the relative magnitude of SD1 compared to SD2 increases and SD12 becomes larger (Fig. 2, top panel). In addition, if the plot is small and ball-shaped because of relatively constant R-R intervals, SD12 also will be large. This measure has not been used much for risk stratification, but has proved useful for detecting editing problems that significantly influence the calculation of HRV variables.

Heart Rate Turbulence

Heart rate turbulence is a novel analytic method, which evaluates the perturbation (shortening then lengthening) in R-R intervals following premature ventricular complexes (VPC).[75] Two parameters quantify the response to VPC: turbulence onset (TO) and turbulence slope (TS). Turbulence onset, a decrease in the first two normal R-R intervals following a VPC compared with the two normal R-R intervals just before the VPC, presumably reflects baroreceptor reflex activity induced by a decreased stroke volume and blood pressure during the compensatory pause. Normally, the two R-R intervals after a VPC are shorter than the two normal R-R intervals immediately preceding the VPC. Turbulence slope quantifies the degree of lengthening of R-R intervals following the shortening of R-R intervals immediately after a VPC, again reflecting baroreflex activity.[75] It is calculated by determining the maximum slope of any 5-beat sequence of normal R-R intervals during the 15–20 R-R

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