Heart rate variability: A measure of cardiac autonomic tone

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The beat of the healthy heart is not absolutely regular. It varies as a result of many factors, including exercise and physical and mental stress. In addition, the intervals between normal sinus beats vary periodically because of respiration, blood pressure regulation, thermoregulation, actions of the renin-angiotensin system, circadian rhythms, and other unknown factors. Such periodic rhythms are in fact the predominant source of heart rate variability. By using Holter recordings, these rhythms can be analyzed to provide a sensitive, noninvasive measurement of autonomic input to the heart.

There are two approaches to measurement of heart rate variability (HRV): analysis in the time or in the frequency domain. These measures are based on the analysis of interbeat intervals of normal beats determined from a routine 24-hour ambulatory electrocardiogram. Time domain analysis addresses the question of "How much variability is there?" Time domain values result from simple, statistical calculations performed on the set of interbeat intervals. Frequency domain analysis addresses the question "What are the underlying rhythms?" In the frequency domain, Fourier analysis is used to partition the total variance of the heart rate into the variance accounted for by underlying groups of frequencies, somewhat like decomposing the sound of a symphony orchestra into the underlying notes.

TIME DOMAIN

Time domain indexes are relatively easy to calculate. There are two classes of time domain variables, one based on interbeat intervals and the other based on comparisons of the lengths of adjacent cycles. Those based on interbeat intervals include SDNN (the standard deviation of all normal R-R intervals [that is, N-N intervals]), which has also been called CLV (cycle length variability), and SDANN (the standard deviation of the mean of the 5-minute intervals, averaged over a 24-hour period). A geometric approach to quantifying interbeat interval-based HRV involves measuring the baseline width (in msec) of the main triangle superimposed on the histogram of all interbeat intervals.[1] This method has the advantage of being less dependent on accurate classification of individual beats. Another time domain index of heart rate variability, SDNNIDX, is the average of the SDs of interbeat intervals for each 5-minute interval, an intermediate between long- and short-term variability. These interbeat interval-based measures are broad-based and are influenced by both short-term (for example, respiratory) and long-term (for example, circadian) factors and are measured in milliseconds. The second class of time domain variables based on comparisons of lengths of *adjacent* cycles includes pNN50 (the proportion of adjacent cycles that are >50 msec apart, measured in percent), and r-MSSD (the root mean square successive differences), which is the square root of the averaged sum of squared differences in length between all adjacent N-N cycles. These variables are virtually independent of long-term trends and predominantly reflect vagal tone.[2] Table I summarizes the time domain indexes of HRV.

FREQUENCY DOMAIN

Analysis in the frequency domain is mathematically more complex, and requires a Holter system with an accurate timing track. However, it has been used by a number of investigators.[1, 3, 4] Frequency domain analysis yields information about the amount of the overall variance in heart rate resulting from periodic oscillations of heart rate at various frequencies. Because heart rate (or, more accurately, heart

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period) is measured in milliseconds, variance, which is referred to as the "power" in a portion of the total spectrum of frequencies, is measured in milliseconds squared. Some investigators report spectral "amplitude," which is the square root of power and is measured in milliseconds. Fig. 1 represents a hypothetical analysis in the frequency domain. In this drastically simplified example, total variability is assumed to be a result of only three frequencies, shown superimposed in Fig. 1 *(top left)*: a "high" frequency of 0.25 Hz (15 cycles per minute), a "low" frequency of 0.1 Hz (6 cycles per minute), and a "very low" frequency of 0.016 Hz (1 cycle per minute). Fig. 1 *(top right)* shows the signal that results when the underlying frequencies in Fig. 1 *(top left)* are combined. Finally, Fig. 1 *(bottom left)* shows the result of a Fourier analysis on the signal in Fig. 1 *(top right)*. Note that the original frequencies reappear on the x axis and that the amount of the total signal variance explained by each frequency (which is proportional to the square of the amplitude of the original signal) is represented by the area under each of the power spectral peaks.

Our approach has been to classify the power spectrum into four bands (Table II). High frequency power (HF), which is parasympathetically mediated and represents primarily respiratory variation, is in the 0.15 to 0.4 Hz band.[3] Low frequency power (LF), which is modulated by both the sympathetic and parasympathetic nervous systems and strongly affected by the oscillatory rhythm of the baroreceptor system,[5] is in the 0.04 to 0.15 Hz band. Very low frequency power (VLF, 0.0033 to 0.04 Hz band) and ultra low frequency power (ULF, 1.15×10^{-5} to 0.0033 Hz) may represent the influence of the thermoregulatory,[6] peripheral vasomotor,[6] or renin-angiotensin[7] systems. Measurement of ULF, which contains most of the variance in the 24-hour spectrum, is based on the entire 24-hour recording and also reflects circadian rhythms, whereas VLF may be obtained from a 15-minute sequence of N-N intervals.[8] Total power (TP) is the total variance in the signal and represents the sum of HF, LF, VLF, and ULF. Earlier studies included only the HF and LF spectra, and thus TP determined by this method may grossly underestimate the true TP. Since these power frequency distributions are skewed for statistical purposes, the natural log transform of power values is used.

Not surprisingly, time and frequency domain measures of HRV are related. For every frequency domain measure, there is a time domain measure that strongly correlates with it (>0.85).[2] HF correlates with r-MSSD and pNN50; LF and VLF correlate with SDNNIDX; ULF correlates well with SDNN and SDANN. TP should be identical to the square of SDNN, since both are measures of the total variance in the heart rate signal. Also, indexes of HRV have been shown to be stable, at least over a 3- to 65-day interval, and there is no placebo effect on HRV.[2] This lack of intraindividual variability over time make measurement of HRV an excellent tool for studying autonomic input to the heart.

Table I. Definitions for time domain measures of heart period variability

Variable	*Units*	*Definition*
SDNN	Msec	Standard deviation of all normal R-R intervals in the entire 24-hr ECG recording (also referred to as SDRR or CLV)
SDANN	Msec	Standard deviation of the mean of all 5-min segments of normal R-R intervals of a 24-hr recording
SDNNIDX	Msec	Mean of the standard deviations of all normal R-R intervals for all 5-min segments of a 24-hr ECG recording
pNN50	%	Percent of difference between adjacent normal R-R intervals that are greater than 50 msec computed over the entire 24-hr ECG recording
r-MSSD	Msec	Root mean square successive differences, the square root of the mean of the sum of the squares of differences between adjacent normal R-R intervals over the entire 24-hr ECG recording
Baseline width	Msec	Width of baseline of main triangle superimposed on the histogram of R-R intervals

SUDDEN DEATH

Abnormalities of autonomic input to the heart have been linked to ventricular arrhythmias during myocardial ischemia or congestive heart failure.[9, 10]

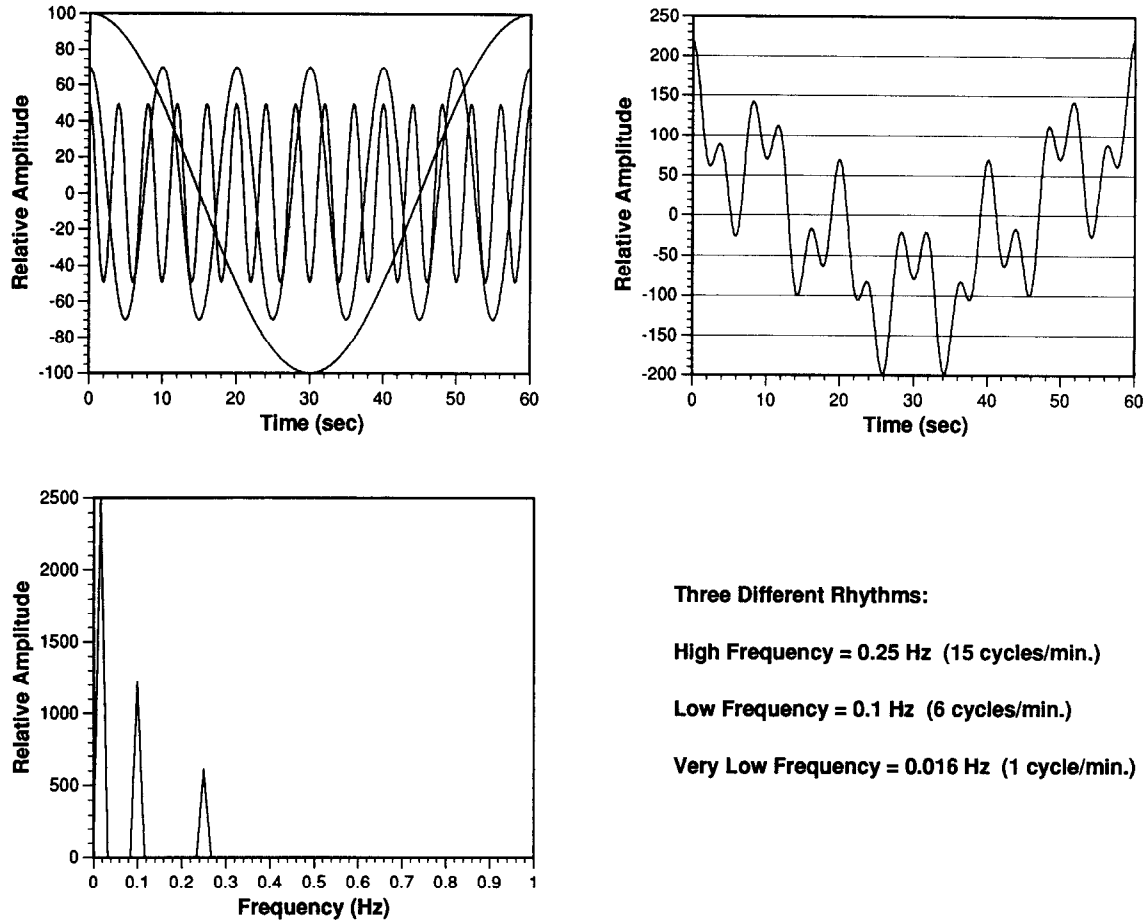

Fig. 1. Top left, Three sinusoidal signals: 1 cycle/min, 6 cycles/min, and 15 cycles/min shown superimposed on the same scale. **Top right,** Same three signals combined into one signal. **Bottom left,** Power spectral analysis of signal shown **top right.**

Table II. Definitions for frequency domain indices of heart rate variability

Variable	*Frequency range*	*Cycles/Time or Time/Cycle*
High frequency power (HF)	0.15-0.40 Hz	9 to 24 cycles/min 2.5 to 6.6 sec/cycle
Low frequency power (LF)	0.04-0.15 Hz	2.4 to 9 cycles/min 6.6 to 25 sec/cycle
Very low frequency power (VLF)	0.0033-0.04 Hz	0.2 to 2.4 cycles/min 25 sec/cycle to 5 min/cycle
Ultra low frequency power (ULF)	$1.15 \times 10^{-5} - 0.0033$ Hz	1 cycle/24 hr to 0.2 cycles/min 24 hr/cycle to 5 min/cycle
Total power (TP)	$1/15 \times 10^{-5} \times 0.40$ Hz	1 cycle/24 hr to 24 cycles/min 24 hr/cycle to 2.5 sec/cycle

Ventricular arrhythmias are accepted as significant precursors to sudden death in patients with ischemic or nonischemic causes of decreased ventricular function. Factors that increase sympathetic or decrease parasympathetic nervous system activity increase the likelihood of ventricular arrhythmias and, conversely, those that decrease sympathetic or increase parasympathetic nervous system activity decrease the likelihood of ventricular arrhythmias.[10, 11] Generally speaking, increased sympathetic or decreased parasympathetic tone are reflected in decreased indices of HRV, while decreased sympathetic or increased parasympathetic nervous system activity are reflected in increased indices of HRV.

Importantly, decreased indices of HRV have shown great value as a predictor of mortality in various clinical populations.[12] Decreased HRV (CLV <50 msec) was reported to be an independent risk factor for mortality post MI by the Multicenter Post

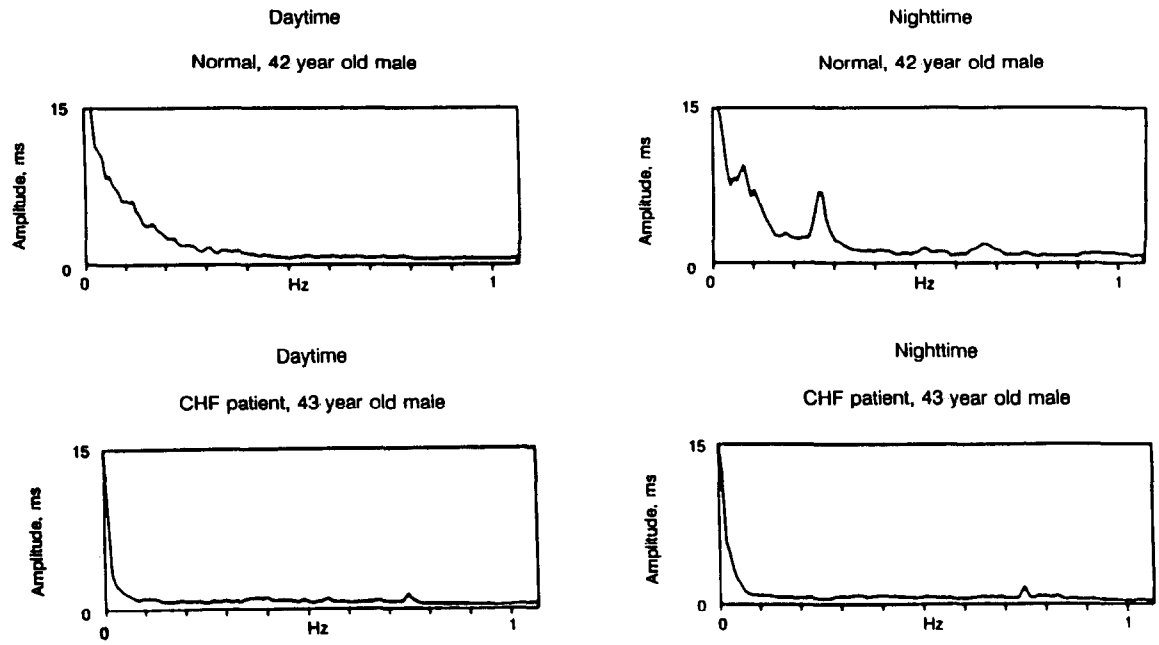

Fig. 2. Top left, One-hour daytime heart period power spectrum for normal 42-year-old man. **Top right,** One-hour nighttime heart period power spectrum for same subject. **Bottom left,** One-hour daytime heart period power spectrum for a 43-year-old patient with congestive heart failure *(CHF)*. **Bottom right,** One-hour nighttime heart period power spectrum for same CHF patient.

Infarction Project (MPIP) in 1987.[13] Since then, numerous investigators have corroborated this finding.[13, 14] In addition, among survivors of acute myocardial infarction (MI), Bigger et al.[15] and Farrell et al.[16] have both shown that decreased HRV predicted both death and arrhythmic events with greater sensitivity and specificity than conventional predictors such as left ventricular ejection fraction. Moreover, HRV parameters in survivors of sudden cardiac death with inducible ventricular tachycardia in the electrophysiology laboratory are markedly decreased compared with those of controls.[17] Low HRV has also been reported to predict mortality among patients undergoing coronary angiography. Rich et al.[18] reported that in 100 stable patients who initially had elective angiography (none had an MI within 4 weeks, nonischemic cardiomyopathy, or valvular disease), SDNN <50 msec was associated with an eighteenfold 1-year mortality compared with patients with an SDNN >50 msec. In patients awaiting cardiac transplantation, SDANN <55 msec identified patients at a twentyfold increased risk of mortality.[19]

CONGESTIVE HEART FAILURE

Furthermore, both time and frequency domain measures of HRV in patients with congestive heart

Table III. Heart rate and heart rate variability from 24-hour Holter recordings for a normal 42-year-old male subject and a 43-year-old male patient with CHF

	Normal subject	*CHF patient*
Average NN (msec)	734	637
SDNN (msec)	170	38
SDANN (msec)	169	31
SDNNIDX (msec)	55	13
r-MSSD (msec)	28	14
pNN50 (%)	6	0
Total power ($msec^2$)	26669	660
Ln total power	10.2	6.5
Ultra low frequency power ($msec^2$)	23861	545
Ln ultra low frequency power	10.1	6.3
Very low frequency power ($msec^2$)	1723	86
Ln very low frequency power	7.5	4.5
Low frequency power ($msec^2$)	834	13
Ln low frequency power	6.7	2.6
High frequency power ($msec^2$)	240	10
Ln high frequency power	5.5	2.3

CHF, Congestive heart failure; *Ln*, natural logarithm; other abbreviations as in Table I.

failure (CHF) have been shown to be markedly diminished compared with HRV in normals.[20-23] Fig. 2 compares spectral power during a 1-hour interval of the day with spectral power during 1 hour of the night for a normal 42-year-old male subject and a 43-year-old patient with congestive heart failure. As can be seen from Fig. 2, although spectral power is lower during the daytime than during the night for the normal subject, for the patient with CHF spectral power is markedly lower than for the normal subject, and equally low during the day and nighttime. Table III compares 24-hour time and frequency domain indices of HRV for the same two individuals.

HRV has also shown predictive value in patients with CHF. Frey et al.[24] found, in a study involving 50 patients with advanced CHF, that two measures, SDNN <70 msec and SDANN <55 msec, predicted 6-month mortality with a sensitivity of 100% and 88%, respectively, and a specificity of 87% in each case. The survivors and nonsurvivors did not differ with respect to hemodynamic measures. In addition, low HRV has been associated with increased risk of mortality among patients with diabetes and alcoholic patients with autonomic neuropathy, infants at risk for sudden infant death syndrome (SIDS), and premature babies.[12]

FUTURE APPLICATIONS

Research into HRV is continuing. The predictive value of HRV for use in risk stratification is being investigated in other patient populations. In addition, the effects of pharmacologic and other interventions on HRV are being explored. It is clear that some medications (for example, digoxin in normals,[25] angiotensin-converting enzyme [ACE] inhibitors in patients with CHF,[26] and atenolol in normals and post-MI patients[27]) increase HRV, while others (for example, class IC antiarrhythmics in normals[28] and patients,[29] pindolol in normals,[30] and imipramine, a tricyclic antidepressant[31]) decrease it. Still others (for example, diltiazem, enalapril, and labetalol[24, 26, 30] in normals, and amiodarone in post-MI patients[31]) have little effect on HRV. Interestingly, medications that decrease HRV have not been shown to improve long-term survival (for example, class IC antiarrhythmic agents). Atenolol in post-MI patients[32] and ACE inhibitors in CHF patients,[33] both of which increase HRV, have been shown to improve survival in these high-risk patients. Although more double-blind and controlled studies need to be conducted, it is quite possible that the effect of pharmacologic manipulations on HRV will become a routine therapeutic consideration, especially for high-risk patients.

Measurement of HRV therefore provides a reliable sensitive, noninvasive measurement of autonomic input to the heart. Clinically, HRV measurements have the potential to identify patients at high risk, especially for sudden death, and to provide detailed information of the autonomic effects of therapy on patients.

SUMMARY

Analysis of HRV based on routine 24-hour Holter recordings provides a sensitive, noninvasive measurement of autonomic input to the heart. HRV can be measured in the time or frequency domain. Each frequency domain variable correlates at least $r = 0.85$ with a time domain variable. Thus time domain measures can be used as surrogates for frequency domain measures which may simplify future studies. Abnormalities of autonomic input to the heart, which are indicated by decreased indices of HRV, are associated with increased susceptibility to ventricular arrhythmias. Decreased indices of HRV are also associated with CHF, diabetes, and alcoholic cardiomyopathy. Decreased indices of HRV are an independent risk factor for mortality post MI and in patients with advanced CHF. Medications can also affect HRV, and that effect may become an important clinical consideration, especially in high-risk patients.

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