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

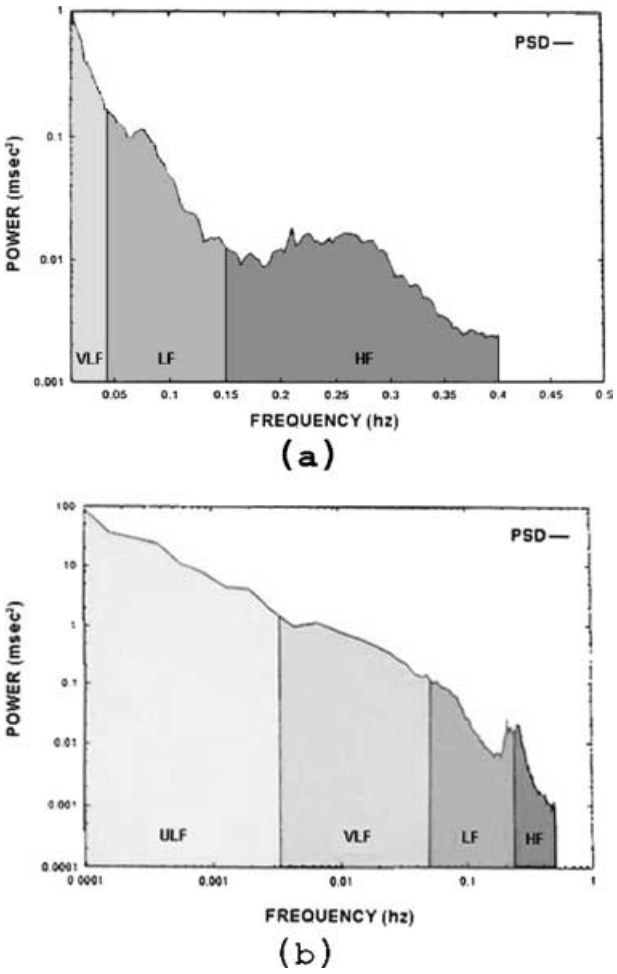

Figure 1. R-R interval power spectra. The upper panel plots log power versus frequency for a 5-minute periodogram and the lower panel plots log power versus frequency for a 24-hour periodogram. In the lower panel, frequency is plotted on a log scale and the Y axis is markedly compressed compared with 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

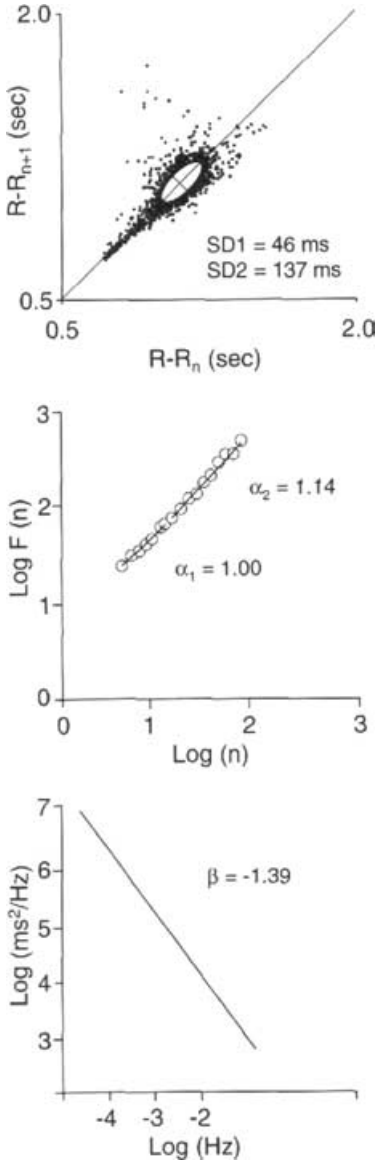

Figure 2. Nonlinear Measures of R-R Interval fluctuations. The top panel shows a two-dimensional vector analysis of a Poincaré plot; the middle panel shows calculation of detrended fluctuation analysis (DFA); and the bottom panel shows calculation of the power law slope. The Poincaré plots and DFA analyses 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 intervals after the VPC. Turbulence onset and

turbulence slope are calculated from all single VPC in a 24-hour recording. Schmidt recommends that at least 5 VPC be present in a Holter recording, in order to estimate heart rate turbulence.[74] Reduced heart rate turbulence is strongly associated with increased death rates after MI.[75–77] Heart rate turbulence will be discussed in detail elsewhere in this journal.

DIAGNOSTIC USES FOR HEART RATE VARIABILITY

Analysis of HRV has been used to assess autonomic function and/or to quantify risk in a wide variety of both cardiac and noncardiac disorders. These include, among others, stroke, multiple sclerosis, end stage renal disease, neonatal distress, diabetes mellitus, ischemic heart disease, particularly myocardial infarction, cardiomyopathy, patients awaiting cardiac transplantation, valvular heart disease, and congestive heart failure.[3,11,12,14,15,17–24,27–29,32,33,35–37,39,43,47,49,50,52] Several authors have reported that HRV analysis is a more sensitive indicator of autonomic dysfunction in alcoholics and in diabetic subjects than conventional autonomic tests.[78–81] Heart rate variability analysis has also been used to assess the autonomic effects of drugs, including beta-blockers, calcium blockers, antiarrhythmics, psychotropic agents, and cardiac glycosides.[65–67,82–91] Drug effects on HRV can be established with relatively small numbers of study participants because HRV measurements are quite stable over the short- and long-term.[92,93]

Heart rate variability analysis has had its greatest cardiologic use in post MI risk stratification and in assessing risk for arrhythmic events. Wolff et al. in 1978 first observed that HR variability measured on admission to the coronary care unit was a predictor of mortality.[94] They calculated the variance of 30 consecutive R-R intervals taken from a 1 minute ECG recording in 176 patients with acute myocardial infarction. The group of patients (n = 73) with R-R interval variance <32 ms had significantly higher hospital mortality than the group with preserved sinus arrhythmia (n = 103). Clinically, patients with low HRV were older, more likely to have an anterior infarct, and more likely to have heart failure. It was not clear from this study whether decreased HRV was an independent predictor of adverse outcome or if it predicted long-term risk after myocardial infarction.

The first study that clearly documented the independent and long-term predictive value of HRV analysis after myocardial infarction was reported in 1987 by the Multi-Center Post-Infarction Program (MPIP).[28] Eight hundred and eight patients who had survived acute myocardial infarction had 24-hour ambulatory electrocardiograms prior to discharge. Besides Holter variables, which included mean heart rate, ventricular arrhythmias, and SDNN, patients were evaluated clinically, had a radionuclide ejection fraction determined and were evaluated by a low level exercise test. During a mean follow up of 31 months, there were 127 deaths (Fig. 3). Forty-three of these deaths occurred in the group of patients with SDNN <50 ms (125 patients), approximately 16% of the total group. Thus, over a third of these patients died during follow-up and a third of the deaths occurred in the group with SDNN <50 ms, establishing a sensitivity and positive predictive accuracy of about one third (Table 3). The relative risk of mortality in patients with SDNN <50 ms versus those with SDNN ≥50 ms was 2.8. Reduced SDNN was significantly associated with low ejection fraction, poor exercise performance, high New York Heart Association functional class, and short R-R intervals (Table 4), but the correlations were weak (0.15–0.52). Multivariate analysis clearly demonstrated that SDNN was an independent risk factor for mortality. SDNN also was the Holter variable with the strongest association with

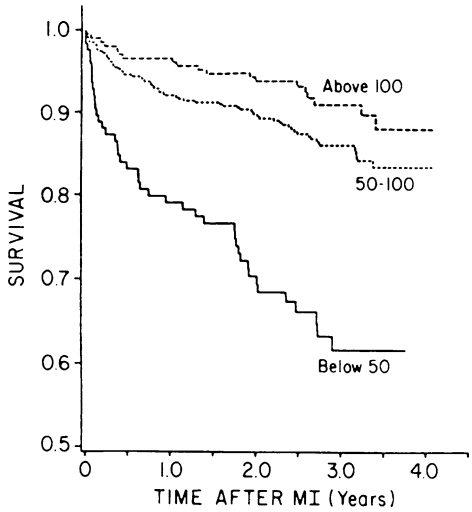

Figure 3. Kaplan-Meier survival curves from the Multi-Center Post-Infarction Study demonstrating decreased survival among patients with SDNN <50 ms (from Ref.28)

Table 3. SDNN Prediction of Mortality in MPIP

	SDNN	
	<50 ms	≥50 ms
Number of patients	125 (15.5%)	683 (84.5%)
Deaths, number (%)	43 (34.4%)	84 (12.3%)
Sensitivity	33.9% (43/127)	
Specificity	88.0% (599/681)	
Positive predictive accuracy	34.4% (43/125)	
False negative rate	12.3% (84/683)	
Relative risk = 2.8 (34.4%/12.3%)		

all-cause mortality, exceeding that of any ventricular arrhythmia measure. Using combinations of risk variables such as SDNN and ejection fraction or SDNN and repetitive VPC subgroups of MI patients could be determined with either very high (50%) mortality or very low (<2%) 31 months mortality.[28,29]

Multi-Center Post-Infarction Program data have been analyzed using other HRV measures. Bigger et al. evaluated the predictive value of 24-hour spectral measures.[9–11] Because of the previously cited physiologic associations of various frequency bands, it was thought that spectral analysis might provide mechanistic insight into death and arrhythmias after myocardial infarction. The anticipated selectivity was not found. All four frequency bands predicted all-cause and arrhythmic mortality, but ultra-low frequency power had the strongest association with these fatal outcomes. Frequency domain measures of HRV had similar predictive value for death of all causes, cardiac death, and arrhythmic death. The MPIP data also have been analyzed using heart rate turbulence, which in the MPIP data set is even a stronger risk predictor than conventional time or frequency domain variables.[75]

Table 4. Correlations of SDNN with Other Variables in MPIP

	r	P
Age	−0.19	0.0001
Rales in the CCU	−0.25	0.0001
Peak BUN	−0.15	0.0007
Ejection fraction	0.24	0.0001
Duration of exercise test	0.15	0.0007
Twenty-four-hour average RR interval	0.52	0.0001
Ln VPC frequency	−0.12	0.0004
Ln ventricular paired VPC	−0.07	0.04
Ln ventricular runs per hour	−0.02	0.57

Multi-Center Post-Infarction Program was done in the late 1970s, prior to the institution of much of what is standard therapy today. Few of the patients received aspirin or B-blockers and none had reperfusion therapy, thrombolytics, angioplasty, or coronary artery bypass graft surgery. Thus, the question arose as to whether the MPIP results apply in the era of reperfusion. Multiple studies since MPIP have confirmed the power of HRV analysis in risk stratification post infarction. Some of these are summarized in Table 5.

Some of the most important of these studies were performed at St. George's hospital in London by Camm, Malik and co-investigators.[19,33,34,37,54] Farrell reported 68 patients with acute myocardial infarction who had both baroreceptor sensitivity and HRV determined before discharge from hospital.[95] The latter was measured using HRV triangular index. Both BRS and HRV index were determined to be good risk stratifiers for survival; BRS was superior. Subsequently, these investigators extended their studies to over 400 survivors of myocardial infarction. In all these studies, they utilized HRV index.[19,37,54] Approximately 60% of their patients received thrombolytic therapy or angioplasty. Besides HRV index, late potentials, ejection fraction, clinical variables, and ventricular arrhythmias were measured. In addition, the mechanisms of death, arrhythmic or nonarrhythmic, and malignant ventricular rhythms were adjudicated. Decreased HRV index best predicted both total cardiac mortality and malignant arrhythmias better than decreased ejection fraction, abnormal late potentials, or increased frequency of ventricular ectopy in 24-hour Holter ECG recordings. Furthermore, combining decreased HRV index with another risk variable, such as decreased ejection fraction or abnormal late potentials, created subgroups of post MI patients with high risk as well as subgroups with very low risk of death or malignant ventricular arrhythmias.[19]

The GISSI study of thrombolytic therapy in acute myocardial infarction evaluated HRV.[52] In GISSI, all 12,490 patients were treated with streptokinase. A subset of 567 patients had a valid 24-hour ambulatory ECG recording and 52 of them died during a 1000-day follow-up. Time domain analysis utilizing SDNN, NN50+, and rMSSD identified high risk groups comprising 16–18% of the subset with mortalities ranging from 20.8 to 24.2% in the high risk

Table 5. Representative Post-MPIP Confirmatory Studies of HRV as a Predictor of All-Cause or Cardiac Mortality After MI. Number in Parenthesis Refers to Reference List. Others Referenced Below Table

Source (Study Name)	Number of Patients (Events)	HRV Measure When Obtained	Follow-Up	HRV Predictors/ Endpoints
Bigger et al. (CAPS)[96]	N = 331 (30 deaths)	24-hour, 1 year after enrolling in CAPS and 1 week after stopping meds	3 years	ULF, VLF, LF, HF all significant, univariate predictors of all-cause mortality. After adjustment for covariates, VLF was the strongest predictor
Copie et al.[97]	N = 579, (54 deaths, 42 cardiac, 26 sudden)	24-hour, before discharge (median 7 days after MI)	> 2 years	HRV index better predictor than mean RR interval for sensitivity <40%. For sensitivity ≥40% mean R-R interval and HRV index equal. Mean R-R interval <700 ms predicted cardiac death (45% sensitivity, 85% specificity, 20% PPA) and predicted all-cause, cardiac and sudden death better than LVEF
Fei et al.[98]	N = 700 (45 cardiac deaths, 24 sudden)	24-hour, 5-minute period, 5–8 days before discharge	1 year	SDNN for 5-minutes had lower PPA than HRV index, but could preselect those who require 24-hour Holter ECG for risk stratification
Huikuri et al. (DIAMOND-MI)[74]	N = 446 with LVEF ≤ 0.35, 114 deaths, 75 arrhythmic, 28 nonarrhythmic	24-hour, predischarge, traditional and nonlinear HRV	685 ± 360 days	α_1 <0.75 RR 3.0, 95% CI 2.5–4.2 for all cause mortality, independent predictor after adjustment. Predicted by arrhythmic and nonarrhythmic death
La Rovere et al. (ATRAMI)[99]	N = 1284 (44 cardiac deaths, 5 nonfatal sudden)	24-hour, <28 days after MI	21 ± 8 months	SDNN <70 ms vs SDNN ≥70 ms
Mäkikallio et al. (TRACE)[100]	N = 159 with LVEF ≤ 35, 72 deaths	24-hour, traditional and nonlinear	4 years	α_1 <0.85 best univariate predictor of mortality (RR 3.17, 95% CI 1.96–5.15), PPA 65% and NPA 86%. Remained significant after adjustment
Odemuyiwa et al.[101]	N = 433 (first MI), (46 total deaths, 15 sudden deaths)	24-hour, before discharge	4 weeks to 5 years	HRV index <20 univariate predictor of mortality for whole follow-up but independent predictor of total cardiac mortality for first 6 months only
Odemuyiwa et al.[37]	N = 385 (44 deaths, 14 sudden)	24-hour, before discharge	151–1618 days	HRV index <39 sensitivity 75%, specificity 52% compared with LVEF ≤40% which had specificity of 40% for all-cause mortality. HRV + LVEF better specificity for sensitivity <60%

Continued

Table 5. Continued.

Source (Study Name)	Number of Patients (Events)	HRV Measure When Obtained	Follow-Up	HRV Predictors/ Endpoints
Quintana et al.[102]	N = 74 (18 deaths 9 nonfatal MI), 24 normal controls	24-hour, mean 4 days after MI	36 ± 15 months	LnVLF <5.99 independent predictor of all-cause mortality (RR = 1.9) or mortality/nonfatal infarction (RR = 2.2)
Tapanainen et al.[103]	N = 697, 49 deaths	24-hour, 2–7 days after MI	18.4 ± 6.5 months	α_1 <0.65 most powerful predictor of mortality RR 5.05, 95% CI 2.87–8.89). After adjustment, α(1) remained independently associated with mortality (RR = 3.90, 95% CI 2.03–7.49)
Touboul et al. (GREPI)[104]	N = 471 (26 deaths for 1 year FU, 39 for long-term FU, 9 sudden) 45% had thrombolysis	24-hour HRV, 10 days after MI	1 year and long term (median 31.4 months)	Nighttime AVGNN <750 ms (RR = 3.2), daytime SDNN <100 ms (RR = 2.6)
Viashnav et al.[105]	N = 226 (19 cardiac deaths)	24-hour, mean 83 hours after MI	Mean 8 months	Cox regression not performed Decreased SDNN, SDANN, ASDNN, LF, HF, LF/HF among nonsurvivors, but rMSSD and pNN50 not different
Voss et al.[106]	N = 572 (43 all-cause, 14 sudden arrhythmic, 22 sudden, 34 cardiac, 13 nonfatal VT/VF)	24-hour, 5–8 days after MI, standard, nonlinear HRV	2 years	For best combination of predictors maximum specificity at 70% sensitivity where PPA for endpoints was 16–29% compared with 6–17% for HRV alone
Zabel et al.[107]	N = 250 (30 endpoints)	24-hour HRV, stable, before discharge	Mean 32 months	SDNN significantly higher in event-free (no VT, resuscitated VF, or death)
Zuanetti et al. (GISSI)[52]	N = 567 males treated with thrombolysis (52 total deaths, 44 cardiac deaths)	24-hours at discharge (median 13 days)	1000 days	Independent predictors of all-cause mortality: NN50 + (RR = 3.5), SDNN (RR = 3.0), rMSSD (RR = 2.8)

ATRAMI = Autonomic Tone and Reflexes after Myocardial Infarction; CAPS = Cardiac Arrhythmia Pilot Study; DIAMOND = Danish Investigations of Arrhythmia and Mortality on Dofetilide; GISSI = Grupo Italiano per lo Studio della Sopravvivenza nell-Infarto Miocardico; GREPI = Groupe d'Etude du Pronostic de l'Infarctus du Myocarde; FU = follow-up; HRV = heart rate variability; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PPA = positive predictive accuracy; RR = relative risk; TRACE = TRAndolapril Cardiac Evaluation; VF = ventricular fibrillation; VT = ventricular tachycardia.

group versus 6.0–6.8% in the low risk group defined by HRV analysis. The relative risk of mortality was approximately 3.0 for the low HRV groups. This study not only confirmed the ability of HRV analysis to risk stratify patients in the modern era of myocardial infarction treatment but also demonstrated that HRV analysis alone has limited positive predictive accuracy.[52]

THERAPEUTIC IMPLICATIONS OF HEART RATE VARIABILITY ANALYSIS

The therapeutic implications to be derived from HRV analysis after myocardial infarction are unclear. Animal models of experimental ischemia and myocardial infarction show a strong association between decreased HRV and spontaneous ventricular fibrillation, decreased ventricular fibrillation threshold and mortality. Furthermore, procedures that increase HRV such as β-adrenergic receptor blockade, exercise conditioning, low dose atropine, or scopolamine administration reduce mortality rates, increase VF threshold, and decrease spontaneous, exercise induced, or ischemia induced ventricular fibrillation in animal models.[15,24,26,40,65–67,69,82–84,108–110] In human studies, β-blockade increase HRV in both healthy persons and patients who have had myocardial infarction,[82–84] as does scopolamine.[109] Type 1C antiarrhythmic drugs decrease HRV.[86,87] Scopolamine in animal models and β-blockers in both animal models and humans improve survival after myocardial infarction, whereas 1C antiarrhythmic drugs increase mortality rates; however, how these effects are related to HRV is not established. Thus, diminished HRV is associated with increased sympathetic and decreased vagal modulation, and these autonomic changes have been associated with an increase in malignant ventricular arrhythmias.[108,110,111]

Perhaps the greatest potential therapeutic use for HRV analysis in patients after myocardial infarction is risk stratification for antiarrhythmic therapy. The European Myocardial Infarct Amiodarone Trial (EMIAT) randomized 1486 post MI patients with ejection fraction $\leq$0.40, age $\leq$75 to amiodarone or placebo therapy.[112] The 743 patients on amiodarone had exactly the same mortality as those on placebo with superimposable Kaplan-Meier mortality curves, but the mechanisms of death was predominantly arrhythmic in the placebo group and nonarrhythmic in the amiodarone treated group. However, in those patients with a low HRV defined as SDNN <50 ms or HRV index $\leq$20 units, there was both a 66% reduction in arrhythmic death and a 24%, borderline significant, decrease in total mortality in the group treated with amiodarone.[113] These results need confirmation but suggest that HRV analysis may be useful in determining which patients with low ejection fractions after myocardial infarction might most benefit from ICD implantation.

The Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) epidemiological study followed 1071 patients after myocardial infarction to evaluate the predictive value of LVEF, BRS, and SDNN after myocardial infarction.[99] Therapy in this study was modern, with 63% of the patients receiving reperfusion therapy. The patients were low risk because those with heart failure or angina were excluded. The average follow up was 21 $\pm$ 8 months. There were 43 cardiac deaths, 5 patients had nonfatal cardiac arrest, and 30 patients had sudden death and/or sustained ventricular tachycardia. LVEF <0.35, SDNN <70 ms, and BRS <3.0 were all associated with cardiac death, sudden death, and nonfatal cardiac arrest. Both BRS and SDNN predicted mortality during follow-up after infarction. In patients under age 65, BRS was a slightly better predictor than SDNN. However, for those over age 65, SDNN predicted death much better than BRS. Baroreflex sensitivity and heart rate variability had independent predictive value, although they were significantly associated. The subgroup that had both low BRS and low HRV had an 18% mortality versus <2% for the group with high values for both variables. It is clear from these data that depressed HRV remains a statistically powerful predictor of death despite modern treatment for myocardial infarction.[114] In ATRAMI, an ejection fraction <0.35 and decreased BRS or HRV defined, even in this low risk group of MI patients, a subgroup with a high, approximately 20%, 2-year mortality.[99]

LIMITATIONS OF HEART RATE VARIABILITY AS A RISK STRATIFIER AFTER MYOCARDIAL INFARCTION

Although decreased HRV is the most powerful ambulatory ECG predictor of cardiac mortality and malignant arrhythmias following

myocardial infarction, and in some studies is a more powerful predictor than ejection fraction, late potentials, and clinical variables, it has several significant limitations. It requires normal sinus rhythm and reasonable signal quality. Atrial fibrillation, sinoatrial dysfunction, and >20% ectopic complexes preclude its use. For heart rate turbulence analysis, five or more VPC are needed in addition to sinus rhythm. To get useful recordings requires great care in applying electrodes to reduce artifact and careful editing of the recording to exclude ectopic complexes and artifacts from the calculations. The best predictors require rather long recording periods in order to include both nighttime and daytime periods. The optimal time after myocardial infarction to measure HRV is not certain. There is considerable recovery of HRV in the 3–6 months after myocardial infarction, but recovery values of HRV are, on average, well below normal age and gender matched healthy individuals.[72,115] Although most studies have been performed in the subacute phase of infarction, some have been performed as late as a year post infarct and HRV remained significantly associated with subsequent mortality.[96]

The best HRV variable to measure is unclear; conventional time domain, BRS, heart rate turbulence, spectral measures, geometric measures, and a variety of nonlinear variables reflect different aspects of HRV and have all been significantly associated with outcome without clear, consistent superiority for any. Moreover, isolated HRV measurements have limited predictive accuracy. As a univariate predictor, HRV has low sensitivity and low positive predictive accuracy. Thus, the therapeutic implications of abnormal HRV are uncertain. Yet it has clearly been demonstrated that combining HRV with other risk variables, such as ejection fraction, BRS, late potentials, exercise testing, or ventricular arrhythmias can define subgroups of patients with both very low and very high total cardiac and arrhythmic mortality after myocardial infarction. HRV in combination with other variables, e.g., left ventricular ejection fraction, may be a very useful clinical tool to better define patients likely or unlikely to benefit from prophylactic ICD implantation.

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