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Heart Rate Variability

Standards of Measurement, Physiological Interpretation, and Clinical Use

Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology

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The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death.[1234] Experimental evidence for an association between propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has spurred efforts for the development of quantitative markers of autonomic activity.

HRV represents one of the most promising such markers. The apparently easy derivation of this measure has popularized its use. As many commercial devices now provide an automated measurement of HRV, the cardiologist has been provided with a seemingly simple tool for both research and clinical studies.[5] However, the significance and meaning of the many different measures of HRV are more complex than generally appreciated, and there is a potential for incorrect conclusions and for excessive or unfounded extrapolations.

Recognition of these problems led the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute a Task Force charged with the responsibility of developing appropriate standards. The specific goals of this Task Force were to (1) standardize nomenclature and develop definitions of terms, (2) specify standard methods of measurement, (3) define physiological and pathophysiological correlates, (4) describe currently appropriate clinical applications, and (5) identify areas for future research.

To achieve these goals, the members of the Task Force were drawn from the fields of mathematics, engineering, physiology, and clinical medicine. The standards and proposals offered in this text should not limit further development but should allow appropriate comparisons, promote circumspect interpretations, and lead to further progress in the field.

The phenomenon that is the focus of this report is the oscillation in the interval between consecutive heartbeats as well as the oscillations between consecutive instantaneous heart rates. “Heart rate variability” has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals. To describe oscillation in consecutive cardiac cycles, other terms have been used in the literature, for example, cycle length variability, heart period variability, RR variability, and RR interval tachogram, and they more appropriately emphasize the fact that it is the interval between consecutive beats that is being analyzed rather than the heart rate per se. However, these terms have not gained as wide acceptance as HRV; thus, we will use the term HRV in this document.

Background

The clinical relevance of HRV was first appreciated in 1965 when Hon and Lee[6] noted that fetal distress was preceded by alterations in interbeat intervals before any appreciable change occurred in heart rate itself. Twenty years ago, Sayers[7] and others[8910] focused attention on the existence of physiological rhythms imbedded in the beat-to-beat heart rate signal. During the 1970s, Ewing et al[11] devised a number of simple bedside tests of short-term RR differences to detect autonomic neuropathy in diabetic patients. The association of higher risk of postinfarction mortality with reduced HRV was first shown by Wolf et al[12] in 1977. In 1981, Akselrod et al[13] introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control.

These frequency domain analyses contributed to the understanding of autonomic background of RR interval fluctuations in the heart rate record.[1415] The clinical importance of HRV became appreciated in the late 1980s, when it was confirmed that HRV was a strong and independent predictor of mortality after an acute myocardial infarction.[161718] With the availability of new, digital, high-frequency, 24-hour, multichannel ECG recorders, HRV has the potential to provide additional valuable insight into physiological and pathological conditions and to enhance risk stratification.

Measurement of HRV

Time Domain Methods

The variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. In these methods, either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous ECG record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate is determined. Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, the difference between night and day heart rate, and so forth. Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, Valsalva maneuver, or phenylephrine infusion. These differences can be described as either differences in heart rate or cycle length.

Statistical Methods

From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods, traditionally 24 hours, more complex statistical time domain measures can be calculated. These may be divided into two classes: (1) those derived from direct measurements of the NN intervals or instantaneous heart rate and (2) those derived from the differences between NN intervals. These variables may be derived from analysis of the total ECG recording or may be calculated using smaller segments of the recording period. The latter method allows comparison of HRV to be made during varying activities, for example, rest, sleep, and so on.

The simplest variable to calculate is the standard deviation of the NN intervals (SDNN), that is, the square root of variance. Since variance is mathematically equal to total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. In many studies SDNN is calculated over a 24-hour period and thus encompasses short-term HF variations as well as the lowest-frequency components seen in a 24-hour period. As the period of monitoring decreases, SDNN estimates shorter and shorter cycle lengths. It also should be noted that the total variance of HRV increases with the length of analyzed recording.[19] Thus, on arbitrarily selected ECGs, SDNN is not a well-defined statistical quantity because of its dependence on the length of recording period. In practice, it is inappropriate to compare SDNN measures obtained from recordings of different durations. On the contrary, durations of the recordings used to determine SDNN values (and similarly other HRV measures) should be standardized. As discussed further in this document, short-term 5-minute recordings and nominal 24-hour long-term recordings appear to be appropriate options.

Other commonly used statistical variables calculated from segments of the total monitoring period include SDANN, the standard deviation of the average NN intervals calculated over short periods, usually 5 minutes, which is an estimate of the changes in heart rate due to cycles longer than 5 minutes, and the SDNN index, the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours, which measures the variability due to cycles shorter than 5 minutes.

The most commonly used measures derived from interval differences include RMSSD, the square root of the mean squared differences of successive NN intervals, NN50, the number of interval differences of successive NN intervals greater than 50 ms, and pNN50, the proportion derived by dividing NN50 by the total number of NN intervals. All of these measurements of short-term variation estimate high-frequency variations in heart rate and thus are highly correlated (Fig 1).

Geometric Methods

The series of NN intervals also can be converted into a geometric pattern such as the sample density distribution of NN interval durations, sample density distribution of differences between adjacent NN intervals, Lorenz plot of NN or RR intervals, and so forth, and a simple formula is used that judges the variability on the basis of the geometric and/or graphics properties of the resulting pattern. Three general approaches are used in geometric methods: (1) a basic measurement of the geometric pattern (for example, the width of the distribution histogram at the specified level) is converted into the measure of HRV, (2) the geometric pattern is interpolated by a mathematically defined shape (for example, approximation of the distribution histogram by a triangle or approximation of the differential histogram by an exponential curve) and then the parameters of this mathematical shape are used, and (3) the geometric shape is classified into several pattern-based categories that represent different classes of HRV (for example, elliptic, linear, and triangular shapes of Lorenz plots). Most geometric methods require the RR (or NN) interval sequence to be measured on or converted to a discrete scale that is not too fine or too coarse and permits the construction of smoothed histograms. Most experience has been obtained with the length of the bins of approximately 8 ms (precisely 7.8125 ms=1/128 seconds), which corresponds to the precision of current commercial equipment.

The HRV triangular index measurement is the integral of the density distribution (that is, the number of all NN intervals) divided by the maximum of the density distribution. Using a measurement of NN intervals on a discrete scale, the measure is approximated by the value (total number of NN intervals)/(number of NN intervals in the modal bin), which is dependent on the length of the bin, that is, on the precision of the discrete scale of measurement. Thus, if the discrete approximation of the measure is used with NN interval measurement on a scale different from the most frequent sampling of 128 Hz, the size of the bins should be quoted. The triangular interpolation of NN interval histogram (TINN) is the baseline width of the distribution measured as a base of a triangle approximating the NN interval distribution (the minimum square difference is used to find such a triangle). Details of computing HRV triangular index and TINN are shown in Fig 2. Both these measures express overall HRV measured over 24 hours and are more influenced by the lower than by the higher frequencies.[17] Other geometric methods are still in the phase of exploration and explanation.[2021]

The major advantage of the geometric methods lies in their relative insensitivity to the analytical quality of the series of NN intervals.[22] The major disadvantage of the geometric methods is the need for a reasonable number of NN intervals to construct the geometric pattern. In practice, recordings of at least 20 minutes (but preferably 24 hours) should be used to ensure the correct performance of the geometric methods; that is, the current geometric methods are inappropriate to assess short-term changes in HRV.

Summary and Recommendations

The variety of time domain measures of HRV is summarized in Table 1. Since many of the measures correlate closely with others, the following four measures are recommended for time domain HRV assessment (1) SDNN (estimate of overall HRV), (2) HRV triangular index (estimate of overall HRV), (3) SDANN (estimate of long-term components of HRV), and (4) RMSSD (estimate of short-term components of HRV).

Two estimates of the overall HRV are recommended because the HRV triangular index permits only casual preprocessing of the ECG signal. The RMSSD method is preferred to pNN50 and NN50 because it has better statistical properties.

The methods expressing overall HRV and its long- and short-term components cannot replace each other. The selection of method used should correspond to the aim of each particular study. Methods that might be recommended for clinical practices are summarized in “Clinical Use of HRV.”

Distinction should be made between measures derived from direct measurements of NN intervals or instantaneous heart rate and from the differences between NN intervals.

It is inappropriate to compare time domain measures, especially those expressing overall HRV, obtained from recordings of different durations.

Other practical recommendations are listed in “Recording Requirements,” together with suggestions related to the frequency analysis of HRV.

Frequency Domain Methods

Various spectral methods[23] for the analysis of the tachogram have been applied since the late 1960s. Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency. Independent of the method used, only an estimate of the true PSD of the signal can be obtained by proper mathematical algorithms.

Methods for the calculation of PSD may be generally classified as nonparametric and parametric. In most instances, both methods provide comparable results. The advantages of the nonparametric methods are (1) the simplicity of the algorithm used (fast Fourier transform [FFT] in most of the cases) and (2) the high processing speed, while the advantages of parametric methods are (1) smoother spectral components that can be distinguished independent of preselected frequency bands, (2) easy postprocessing of the spectrum with an automatic calculation of low- and high-frequency power components with an easy identification of the central frequency of each component, and (3) an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationarity. The basic disadvantage of parametric methods is the

need of verification of the suitability of the chosen model and of its complexity (that is, the order of the model).

Spectral Components

Short-term recordings. Three main spectral components are distinguished in a spectrum calculated from short-term recordings of 2 to 5 minutes[7,10,13,15,24] : VLF, LF, and HF components. The distribution of the power and the central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of heart period.[15,24,25] The physiological explanation of the VLF component is much less defined, and the existence of a specific physiological process attributable to these heart period changes might even be questioned. The nonharmonic component, which does not have coherent properties and is affected by algorithms of baseline or trend removal, is commonly accepted as a major constituent of VLF. Thus, VLF assessed from short-term recordings (≤5 minutes) is a dubious measure and should be avoided when the PSD of short-term ECGs is interpreted.

The measurement of VLF, LF, and HF power components is usually made in absolute values of power (milliseconds squared). LF and HF may also be measured in normalized units,[15,24] which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in normalized units emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system. Moreover, the normalization tends to minimize the effect of the changes in total power on the values of LF and HF components (Fig 3). Nevertheless, normalized units should always be quoted with absolute values of the LF and HF power in order to describe completely the distribution of power in spectral components.

Long-term recordings. Spectral analysis also may be used to analyze the sequence of NN intervals of the entire 24-hour period. The result then includes a ULF component, in addition to VLF, LF, and HF components. The slope of the 24-hour spectrum also can be assessed on a log-log scale by linear fitting the spectral values. Table 2 lists selected frequency domain measures.

The problem of “stationarity” is frequently discussed with long-term recordings. If mechanisms responsible for heart period modulations of a certain frequency remain unchanged during the whole period of recording, the corresponding frequency component of HRV may be used as a measure of these modulations. If the modulations are not stable, the interpretation of the results of frequency analysis is less well defined. In particular, physiological mechanisms of heart period modulations responsible for LF and HF power components cannot be considered stationary during the 24-hour period.[25] Thus, spectral analysis performed on the entire 24-hour period as well as spectral results obtained from shorter segments (5 minutes) averaged over the entire 24-hour period (the LF and HF results of these two computations are not different[26,27]) provide averages of the modulations attributable to the LF and HF components (Fig 4). Such averages obscure the detailed information about autonomic modulation of RR intervals that is available in shorter recordings.[25] It should be remembered that the components of HRV provide measurement of the degree of autonomic modulations rather than of the level of autonomic tone,[28] and averages of modulations do not represent an averaged level of tone.

Technical Requirements and Recommendations

Because of the important differences in the interpretation of the results, the spectral analyses of short-term and long-term ECGs should always be strictly distinguished, as reported in Table 2.

The analyzed ECG signal should satisfy several requirements in order to obtain a reliable spectral estimation. Any departure from the following requirements may lead to unreproducible results that are difficult to interpret.

To attribute individual spectral components to well-defined physiological mechanisms, such mechanisms modulating the heart rate should not change during the recording. Transient physiological phenomena may perhaps be analyzed by specific methods that currently constitute a challenging research topic but are not yet ready to be used in applied research. To check the stability of the signal in terms of certain spectral components, traditional statistical tests may be used.[29]

The sampling rate must be properly chosen. A low sampling rate may produce a jitter in the estimation of the R-wave fiducial point, which alters the spectrum considerably. The optimal range is 250 to 500 Hz or perhaps even higher,[30] while a lower sampling rate (in any case ≥100 Hz) may behave satisfactorily only if an algorithm of interpolation (parabolic) is used to refine the R-wave fiducial point.[3132]

Baseline and trend removal (if used) may affect the lower components in the spectrum. It is advisable to check the frequency response of the filter or the behavior of the regression algorithm and to verify that the spectral components of interest are not significantly affected.

The choice of QRS fiducial point may be critical. It is necessary to use a well-tested algorithm (derivative plus threshold, template, correlation method) to locate a stable and noise-independent reference point.[33] A fiducial point localized far within the QRS complex may also be influenced by varying ventricular conduction disturbances.

Ectopic beats, arrhythmic events, missing data, and noise effects may alter the estimation of the PSD of HRV. Proper interpolation (or linear regression or similar algorithms) on preceding/successive beats on the HRV signal or on its autocorrelation function may decrease this error. Preferentially, short-term recordings that are free of ectopy, missing data, and noise should be used. In some circumstances, however, acceptance of only ectopic-free, short-term recordings may introduce significant selection bias. In such cases, proper interpolation should be used and the possibility of the results being influenced by ectopy should be considered.[34] The relative number and relative duration of RR intervals that were omitted and interpolated should also be quoted.

Algorithmic Standards and Recommendations

The series of data subjected to spectral analysis can be obtained in different ways. A useful pictorial representation of the data is the discrete event series (DES), that is, the plot of R_iR_{i-1} interval versus time (indicated at R_i occurrence), which is an irregularly time-sampled signal. Nevertheless, spectral analysis of the sequence of instantaneous heart rates has also been used in many studies.[26]

The spectrum of the HRV signal is generally calculated either from the RR interval tachogram (RR durations versus number of progressive beats; see Fig 5a,b) or by interpolating the DES, thus

obtaining a continuous signal as a function of time, or by calculating the spectrum of the counts–unitary pulses as a function of time corresponding to each recognized QRS complex.[35] Such a choice may have implications on the morphology, the measurement units of the spectra, and the measurement of the relevant spectral parameters. To standardize the methods used, the use of RR interval tachogram with the parametric method, or the use of the regularly sampled interpolation of DES with the nonparametric method may be suggested; nevertheless, regularly sampled interpolation of DES is also suitable for parametric methods. The sampling frequency of interpolation of DES must be sufficiently high that the Nyquist frequency of the spectrum is not within the frequency range of interest.

Standards for nonparametric methods (based on the FFT algorithm) should include the values reported in Table 2, the formula of DES interpolation, the frequency of sampling the DES interpolation, the number of samples used for the spectrum calculation, and the spectral window used (Hann, Hamming, and triangular windows are most frequently used).[36] The method of calculating the power in respect of the window also should be quoted. In addition to requirements described in other parts of this document, each study using the nonparametric spectral analysis of HRV should quote all these parameters.

Standards for parametric methods shall include the values reported in Table 2, the type of the model used, the number of samples, the central frequency for each spectral component (LF and HF), and the value of the model order (numbers of parameters). Furthermore, statistical figures must be calculated in order to test the reliability of the model. The prediction error whiteness test (PEWT) provides information about the goodness of the fitting model,[37] while the optimal order test (OOT) checks the suitability of the order of the model used.[38] There are different possibilities of performing OOT that include final prediction error and Akaike information criteria. The following operative criterion for choosing the order P of an autoregressive model might be proposed: the order shall be in the range of 8 to 20, fulfilling the PEWT test and complying with the OOT test ($P \approx \min[\mathrm{OOT}]$).

Correlation and Differences Between Time and Frequency Domain Measures

In the analysis of stationary short-term recordings, more experience and theoretical knowledge exist on physiological interpretation of the frequency domain measures compared with the time domain measures derived from the same recordings.

On the contrary, many time and frequency domain variables measured over the entire 24-hour period are strongly correlated with each other (Table 3). These strong correlations exist because of both mathematical and physiological relationships. In addition, the physiological interpretation of the spectral components calculated over 24 hours is difficult, namely because of reasons mentioned above (see “Long-term recordings”). Thus, unless special investigations are performed that use the 24-hour HRV signal to extract information other than the usual frequency components (for example, the log-log slope of spectrogram), the results of the frequency-domain analysis are equivalent to those of the time domain analysis, which is easier to perform.

Rhythm Pattern Analysis

As illustrated in Fig 6,[39] the time domain and spectral methods share limitations imposed by the irregularity of the RR series. Clearly different profiles analyzed by these techniques may give

identical results. Trends of decreasing or increasing cycle length are in reality not symmetric[40,41] as heart rate accelerations are usually followed by a faster decrease. In spectral results, this tends to reduce the peak at the fundamental frequency and to enlarge its basis. This leads to the idea of measuring blocks of RR intervals determined by properties of the rhythm and investigating the relationship of such blocks without considering the internal variability.

Approaches derived from the time domain and the frequency domain have been proposed in order to reduce these difficulties. The interval spectrum and spectrum of counts methods lead to equivalent results (Fig 6d) and are well suited to investigate the relationship between HRV and the variability of other physiological measures. The interval spectrum is well adapted to link RR intervals to variables defined on a beat-to-beat basis (blood pressure). The spectrum of counts is preferable if RR intervals are related to a continuous signal (respiration) or to the occurrence of special events (arrhythmia).

The “peak-valley” procedures are based either on the detection of the summit and the nadir of oscillations[42,43] or on the detection of trends of heart rate.[44] The detection may be limited to short-term changes,[42] but it can be extended to longer variations: second- and third-order peaks and troughs[43] or stepwise increase of a sequence of consecutive increasing or decreasing cycles surrounded by opposite trends.[44] The various oscillations can be characterized on the basis of the heart rate acceleration or slowing, the wavelength, and/or the amplitude. In a majority of short- to mid-term recordings, the results are correlated with frequency components of HRV.[45] The correlations, however, tend to diminish as the wavelength of the oscillations and the recording duration increase. Complex demodulation uses the techniques of interpolation and detrending[46] and provides the time resolution necessary to detect short-term heart rate changes as well as to describe the amplitude and phase of particular frequency components as functions of time.

Nonlinear Methods

Nonlinear phenomena are certainly involved in the genesis of HRV. They are determined by complex interactions of hemodynamic, electrophysiological, and humoral variables as well as by the autonomic and central nervous regulations. It has been speculated that analysis of HRV based on the methods of nonlinear dynamics might elicit valuable information for physiological interpretation of HRV and for the assessment of the risk of sudden death. The parameters that have been used to measure nonlinear properties of HRV include 1/f scaling of Fourier spectra,[47,19] H scaling exponent, and Coarse Graining Spectral Analysis (CGSA).[48] For data representation, Poincaré sections, low-dimension attractor plots, singular value decomposition, and attractor trajectories have been used. For other quantitative descriptions, the D_2 correlation dimension, Lyapunov exponents, and Kolmogorov entropy have been used.[49]

Although in principle, these techniques have been shown to be powerful tools for characterization of various complex systems, no major breakthrough has yet been achieved by their application to biomedical data including HRV analysis. It is possible that integral complexity measures are not adequate to analyze biological systems and thus are too insensitive to detect the nonlinear perturbations of RR interval, which would be of physiological or practical importance. More encouraging results have been obtained using differential rather than integral complexity measures,

for example, the scaling index method.[5051] However, no systematic study has been conducted to investigate large patient populations with the use of these methods.

At present, the nonlinear methods represent potential tools for HRV assessment. Standards are lacking, and the full scope of these methods cannot be assessed. Advances in technology and the interpretation of the results of nonlinear methods are needed before these methods are ready for physiological and clinical studies.

Stability and Reproducibility of HRV Measurement

Multiple studies have demonstrated that short-term measures of HRV rapidly return to baseline after transient perturbations induced by such manipulations as mild exercise, administration of short-acting vasodilators, and transient coronary occlusion. More powerful stimuli, such as maximum exercise or administration of long-acting drugs, may result in a much more prolonged interval before return to control values.

There are far fewer data on the stability of long-term measures of HRV obtained from 24-hour ambulatory monitoring. Nonetheless, the limited data available suggest great stability of HRV measures derived from 24-hour ambulatory monitoring in both normal subjects[5253] and in the postinfarction[54] and ventricular arrhythmia[55] populations. There also exist some fragmentary data to suggest that stability of HRV measures may persist for periods of months and years. Because 24-hour indices appear to be stable and free of placebo effect, they may be ideal variables to assess intervention therapies.

Recording Requirements

ECG Signal

The fiducial point recognized on the ECG tracing that identifies a QRS complex may be based on the maximum or baricentrum of the complex, on the determination of the maximum of an interpolating curve, or found by matching with a template or other event markers. To localize the fiducial point, voluntary standards for diagnostic ECG equipment are satisfactory in terms of signal-to-noise ratio, common mode rejection, bandwidth, and so forth.[56] An upper-band frequency cutoff substantially lower than that established for diagnostic equipment (≈200 Hz) may create a jitter in the recognition of the QRS complex fiducial point, introducing an error of measured RR intervals. Similarly, limited sampling rate induces an error in the HRV spectrum that increases with frequency, thus affecting more high-frequency components.[31] An interpolation of the undersampled ECG signal may decrease this error. With proper interpolation, even a 100-Hz sampling rate can be sufficient.[32]

When solid-state storage recorders are used, data compression techniques must be carefully considered in terms of both the effective sampling rate and the quality of reconstruction methods that may yield amplitude and phase distortion.[57]

Duration and Circumstances of ECG Recording

In studies researching HRV, the duration of recording is dictated by the nature of each investigation. Standardization is needed particularly in studies investigating the physiological and clinical potential of HRV.

Frequency domain methods should be preferred to the time domain methods when short-term recordings are investigated. The recording should last for at least 10 times the wavelength of the lower frequency bound of the investigated component, and, in order to ensure the stability of the signal, should not be substantially extended. Thus, recording of approximately 1 minute is needed to assess the HF components of HRV, while approximately 2 minutes are needed to address the LF component. To standardize different studies investigating short-term HRV, 5-minute recordings of a stationary system are preferred unless the nature of the study dictates another design.

Averaging of spectral components obtained from sequential periods of time is able to minimize the error imposed by the analysis of very short segments. Nevertheless, if the nature and degree of physiological heart period modulations changes from one short segment of the recording to another, the physiological interpretation of such averaged spectral components suffers from the same intrinsic problems as that of the spectral analysis of long-term recordings and warrants further elucidation. A display of stacked series of sequential power spectra (for example, over 20 minutes) may help confirm steady state conditions for a given physiological state.

Although the time domain methods, especially the SDNN and RMSSD methods, can be used to investigate recordings of short durations, the frequency methods are usually able to provide results that are more easily interpretable in terms of physiological regulations. In general, the time domain methods are ideal for the analysis of long-term recordings (the lower stability of heart rate modulations during long-term recordings makes the results of frequency methods less easily interpretable). The experience shows that a substantial part of the long-term HRV value is contributed by the day-night differences. Thus, the long-term recording analyzed by the time domain methods should contain at least 18 hours of analyzable ECG data that include the whole night.

Little is known about the effects of the environment (type and nature of physical activity and emotional circumstances) during long-term ECG recordings. For some experimental designs, environmental variables should be controlled and in each study, the character of the environment should always be described. The design of investigations also should ensure that the recording environment of individual subjects is similar. In physiological studies comparing HRV in different well-defined groups, the differences between underlying heart rate also should be properly acknowledged.

Editing of the RR Interval Sequence

The errors imposed by the imprecision of the NN interval sequence are known to affect substantially the results of statistical time domain and all frequency domain methods. It is known that casual editing of the RR interval data is sufficient for the approximate assessment of total HRV by the geometric methods, but it is not known how precise the editing should be to ensure correct results from other methods. Thus, when the statistical time domain and/or frequency domain methods are used, the manual editing of the RR data should be performed to a very high standard, ensuring correct identification and classification of every QRS complex. Automatic “filters” that exclude some intervals from the original RR sequence (for example, those differing by more than 20% from the previous interval) should not replace manual editing because they are known to behave unsatisfactorily and to have undesirable effects leading potentially to errors.[58]

Suggestions for Standardization of Commercial Equipment

Standard measurement of HRV. Commercial equipment designed to analyze short-term HRV should incorporate nonparametric and preferably also parametric spectral analysis. To minimize the possible confusion imposed by reporting the components of the cardiac beat–based analysis in time frequency components, the analysis based on regular sampling of the tachograms should be offered in all cases. The nonparametric spectral analysis should use at least 512 but preferably 1024 points for 5-minute recordings.

Equipment designed to analyze HRV in long-term recordings should implement time domain methods, including all four standard measures (SDNN, SDANN, RMSSD, and HRV triangular index). In addition to other options, the frequency analysis should be performed in 5-minute segments (using the same precision as with the analysis of short-term ECGs). When spectral analysis of the total nominal 24-hour record is performed to compute the whole range of HF, LF, VLF, and ULF components, the analysis should be performed with a similar precision of periodogram sampling as suggested for the short-term analysis, for example, using 2^{18} points.

The strategy of obtaining the data for the HRV analysis should copy the design outlined in Fig 7.

Precision and testing of commercial equipment. To ensure the quality of different equipment involved in HRV analysis and to find an appropriate balance between the precision essential to research and clinical studies and the cost of the equipment required, independent testing of all equipment is needed. Because the potential errors of the HRV assessment include inaccuracies in the identification of fiducial points of QRS complexes, the testing should include all the recording, replay, and analysis phases. Thus, it seems ideal to test various equipment with signals (that is, computer simulated) of known HRV properties rather than with existing databases of already digitized ECGs. When commercial equipment is used in studies investigating physiological and clinical aspects of HRV, independent tests of the equipment used should always be required. A possible strategy for testing of commercial equipment is proposed in “Appendix B.” Voluntary industrial standards should be developed adopting this or similar strategy.

Summary and Recommendations

To minimize the errors caused by improperly designed or incorrectly used techniques, the following points are recommended.

The ECG equipment used should satisfy the current voluntary industrial standards in terms of signal-to-noise ratio, common mode rejection, bandwidth, and so forth.

Solid-state recorders used should allow signal reconstruction without amplitude and phase distortion.

Long-term ECG recorders using analogue magnetic media should accompany the signal with phase-locked time tracking.

Commercial equipment used to assess HRV should satisfy the technical requirements listed in “Standard measurement of HRV,” and its performance should be independently tested.

To standardize physiological and clinical studies, two types of recordings should be used whenever possible: (a) short-term recordings of 5 minutes made under physiologically stable conditions processed by frequency domain methods and/or (b) nominal 24-hour recordings processed by time-domain methods.

When long-term ECGs are used in clinical studies, individual subjects should be recorded under fairly similar conditions and in a fairly similar environment.

When statistical time domain or frequency domain methods are used, the complete signal should be carefully edited using visual checks and manual corrections of individual RR intervals and QRS complex classifications. Automatic “filters” based on hypotheses on the logic of RR interval sequence (for example, exclusion of RR intervals according to a certain prematurity threshold) should not be relied on when the quality of the RR interval sequence is ensured.

Physiological Correlates of HRV

Physiological Correlates of HRV Components

Autonomic Influences of Heart Rate

Although cardiac automaticity is intrinsic to various pacemaker tissues, heart rate and rhythm are largely under the control of the autonomic nervous system.[59] The parasympathetic influence on heart rate is mediated via release of acetylcholine by the vagus nerve. Muscarinic acetylcholine receptors respond to this release mostly by an increase in cell membrane K^+ conductance.[606162] Acetylcholine also inhibits the hyperpolarization-activated “pacemaker” current If.[6364] The “Ik decay” hypothesis[65] proposes that pacemaker depolarization results from slow deactivation of the delayed rectifier current, Ik, which, due to a time-independent background inward current, causes diastolic depolarization.[6566] Conversely, the “If activation” hypothesis[67] suggests that after action potential termination, If provides a slowly activating inward current predominating over decaying Ik, thus initiating slow diastolic depolarization.

The sympathetic influence on heart rate is mediated by release of epinephrine and norepinephrine. Activation of β-adrenergic receptors results in cAMP-mediated phosphorylation of membrane proteins and increases in ICaL[68] and in If.[6970] The end result is an acceleration of the slow diastolic depolarization.

Under resting conditions, vagal tone prevails[71] and variations in heart period are largely dependent on vagal modulation.[72] The vagal and sympathetic activity constantly interact. Because the sinus node is rich in acetylcholinesterase, the effect of any vagal impulse is brief because the acetylcholine is rapidly hydrolyzed. Parasympathetic influences exceed sympathetic effects probably through two independent mechanisms: (1) a cholinergically induced reduction of norepinephrine released in response to sympathetic activity and (2) a cholinergic attenuation of the response to a adrenergic stimulus.

Components of HRV

The RR interval variations present during resting conditions represent a fine tuning of the beat-to-beat control mechanisms.[7374] Vagal afferent stimulation leads to reflex excitation of vagal efferent

activity and inhibition of sympathetic efferent activity.[75] The opposite reflex effects are mediated by the stimulation of sympathetic afferent activity.[76] Efferent vagal activity also appears to be under "tonic" restraint by cardiac afferent sympathetic activity.[77] Efferent sympathetic and vagal activities directed to the sinus node are characterized by discharge largely synchronous with each cardiac cycle that can be modulated by central (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators.[24] These oscillators generate rhythmic fluctuations in efferent neural discharge that manifest as short- and long-term oscillation in the heart period. Analysis of these rhythms may permit inferences on the state and function of (a) the central oscillators, (b) the sympathetic and vagal efferent activity, (c) humoral factors, and (d) the sinus node.

An understanding of the modulatory effects of neural mechanisms on the sinus node has been enhanced by spectral analysis of HRV. The efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy.[131424] More controversial is the interpretation of the LF component, which is considered by some[24787980] as a marker of sympathetic modulation (especially when expressed in normalized units) and by others[1381] as a parameter that includes both sympathetic and vagal influences. This discrepancy is due to the fact that in some conditions associated with sympathetic excitation, a decrease in the absolute power of the LF component is observed. It is important to recall that during sympathetic activation the resulting tachycardia is usually accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation. When the spectral components are expressed in absolute units (milliseconds squared), the changes in total power influence LF and HF in the same direction and prevent the appreciation of the fractional distribution of the energy. This explains why in supine subjects under controlled respiration, atropine reduces both LF and HF[14] and why during exercise LF is markedly reduced.[24] This concept is exemplified in Fig 3, showing the spectral analysis of HRV in a normal subject during control supine conditions and 90° head-up tilt. Because of the reduction in total power, LF appears as unchanged if considered in absolute units. However, after normalization an increase in LF becomes evident. Similar results apply to the LF/HF ratio.[82]

Spectral analysis of 24-hour recordings[2425] shows that in normal subjects, LF and HF expressed in normalized units exhibit a circadian pattern and reciprocal fluctuations, with higher values of LF in the daytime and of HF at night. These patterns become undetectable when a single spectrum of the entire 24-hour period is used or when spectra of subsequent shorter segments are averaged. In long-term recordings, the HF and LF components account for only approximately 5% of total power. Although the ULF and VLF components account for the remaining 95% of total power, their physiological correlates are still unknown.

LF and HF can increase under different conditions. An increased LF (expressed in normalized units) is observed during 90° tilt, standing, mental stress, and moderate exercise in healthy subjects, and during moderate hypotension, physical activity, and occlusion of a coronary artery or common carotid arteries in conscious dogs.[2479] Conversely, an increase in HF is induced by controlled respiration, cold stimulation of the face, and rotational stimuli.[2478]

Summary and Recommendations for Interpretation of HRV Components

Vagal activity is the major contributor to the HF component.

Disagreement exists in respect to the LF component. Some studies suggest that LF, when expressed in normalized units, is a quantitative marker of sympathetic modulations; other studies view LF as reflecting both sympathetic activity and vagal activity. Consequently, the LF/HF ratio is considered by some investigators to mirror sympathovagal balance or to reflect the sympathetic modulations.

Physiological interpretation of lower-frequency components of HRV (that is, of the VLF and ULF components) warrants further elucidation.

It is important to note that HRV measures fluctuations in autonomic inputs to the heart rather than the mean level of autonomic inputs. Thus, both autonomic withdrawal and saturatingly high level of sympathetic input lead to diminished HRV.[28]

Changes of HRV Related to Specific Pathologies

A reduction of HRV has been reported in several cardiological and noncardiological diseases.[24788183]

Myocardial Infarction

Depressed HRV after MI may reflect a decrease in vagal activity directed to the heart, which leads to prevalence of sympathetic mechanisms and to cardiac electrical instability. In the acute phase of MI, the reduction in 24-hour SDNN is significantly related to left ventricular dysfunction, peak creatine kinase, and Killip class.[84]

The mechanism by which HRV is transiently reduced after MI and by which a depressed HRV is predictive of the neural response to acute MI is not yet defined, but it is likely to involve derangements in the neural activity of cardiac origin. One hypothesis[85] involves cardiocardiac sympathosympathetic[8687] and sympathovagal reflexes[75] and suggests that the changes in the geometry of a beating heart due to necrotic and noncontracting segments may abnormally increase the firing of sympathetic afferent fibers by mechanical distortion of the sensory endings.[768788] This sympathetic excitation attenuates the activity of vagal fibers directed to the sinus node. Another explanation, especially applicable to marked reduction of HRV, is the reduced responsiveness of sinus nodal cells to neural modulations.[8285]

Spectral analysis of HRV in patients surviving an acute MI revealed a reduction in total and in the individual power of spectral components.[89] However, when the power of LF and HF was calculated in normalized units, an increased LF and a diminished HF were observed during both resting controlled conditions and 24-hour recordings analyzed over multiple 5-minute periods.[9091] These changes may indicate a shift of sympathovagal balance toward a sympathetic predominance and a reduced vagal tone. Similar conclusions were obtained by considering the changes in LF/HF ratio. The presence of an alteration in neural control mechanisms was also reflected by the blunting of the day-night variations of RR interval[91] and LF and HF spectral components[9192] present in a period ranging from days to a few weeks after the acute event. In post-MI patients with a very depressed HRV, most of the residual energy is distributed in the VLF frequency range below 0.03 Hz, with only a small respiration-related HF.[93] These characteristics of the spectral profile are similar to those

observed in an advanced cardiac failure or after cardiac transplant and are likely to reflect either a diminished responsiveness of the target organ to neural modulatory inputs[82] or a saturating influence on the sinus node of a persistently high sympathetic tone.[28]

Diabetic Neuropathy

In neuropathy associated with diabetes mellitus characterized by alteration of small nerve fibers, a reduction in time domain parameters of HRV seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy.[94959697] In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute power of LF and HF during controlled conditions was also reported.[96] However, when the LF/HF ratio was considered or when LF and HF were analyzed in normalized units, no significant difference in comparison to normal subjects was present. Thus, the initial manifestation of this neuropathy is likely to involve both efferent limbs of the autonomic nervous system.[9698]

Cardiac Transplantation

A very reduced HRV with no definite spectral components was reported in patients with a recent heart transplant.[9799100] The appearance of discrete spectral components in a few patients is considered to reflect cardiac reinnervation.[101] This reinnervation may occur as early as 1 to 2 years after transplantation and is usually of sympathetic origin. Indeed, the correlation between the respiratory rate and the HF component of HRV observed in some transplanted patients also indicates that a nonneural mechanism may contribute to generate a respiration-related rhythmic oscillation.[100] The initial observation of identifying patients developing an allograft rejection according to changes in HRV could be of clinical interest but needs further confirmation.

Myocardial Dysfunction

A reduced HRV has been observed consistently in patients with cardiac failure.[247881102103104105106] In this condition characterized by signs of sympathetic activation such as faster heart rates and high levels of circulating catecholamines, a relation between changes in HRV and the extent of left ventricular dysfunction was reported.[102104] In fact, whereas the reduction in time domain measures of HRV seemed to parallel the severity of the disease, the relationship between spectral components and indices of ventricular dysfunction appears to be more complex. In particular, in most patients with a very advanced phase of the disease and with a drastic reduction in HRV, an LF component could not be detected despite the clinical signs of sympathetic activation. Thus, in conditions characterized by a marked and unopposed persistent sympathetic excitation, the sinus node seems to drastically diminish its responsiveness to neural inputs.[104]

Tetraplegia

Patients with chronic complete high cervical spinal cord lesions have intact efferent vagal and sympathetic neural pathways directed to the sinus node. However, spinal sympathetic neurons are deprived of modulatory control and in particular of baroreflex supraspinal inhibitory inputs. For this reason, these patients represent a unique clinical model to evaluate the contribution of supraspinal mechanisms in determining the sympathetic activity responsible for LF oscillations of HRV. It has been reported[107] that no LF could be detected in tetraplegic patients, thus suggesting the critical role of supraspinal mechanisms in determining the 0.1 Hz rhythm. Two recent studies, however, have indicated that an LF component also can be detected in HRV and arterial pressure variabilities

of some tetraplegic patients.[108][109] While Koh et al[108] attributed the LF component of HRV to vagal modulations, Guzzetti et al[109] attributed the same component to sympathetic activity because of the delay with which the LF component appeared after spinal section, suggesting an emerging spinal rhythmicity capable of modulating sympathetic discharge.

Modifications of HRV by Specific Interventions

The rationale for trying to modify HRV after MI stems from the multiple observations indicating that cardiac mortality is higher among those post-MI patients who have a more depressed HRV.[93][110] The inference is that interventions that augment HRV may be protective against cardiac mortality and sudden cardiac death. Although the rationale for changing HRV is sound, it also contains the inherent danger of leading to the unwarranted assumption that modification of HRV translates directly into cardiac protection, which may not be the case.[111] The target is the improvement of cardiac electrical stability, and HRV is just a marker of autonomic activity. Despite the growing consensus that increases in vagal activity can be beneficial,[112] it is not as yet known how much vagal activity (or its markers) has to increase in order to provide adequate protection.

β-Adrenergic Blockade and HRV

The data on the effect of β-blockers on HRV in post-MI patients are surprisingly scant.[113][114] Despite the observation of statistically significant increases, the actual changes are very modest. However, it is of note that β-blockade prevents the rise in the LF component observed in the morning hours.[114] In conscious post-MI dogs, β-blockers do not modify HRV.[115] The unexpected observation that before MI, β-blockade increases HRV only in the animals destined to be at low risk for lethal arrhythmias after MI[115] may suggest novel approaches to post-MI risk stratification.

Antiarrhythmic Drugs and HRV

Data exist for several antiarrhythmic drugs. Flecainide and propafenone but not amiodarone were reported to decrease time domain measures of HRV in patients with chronic ventricular arrhythmia.[116] In another study,[117] propafenone reduced HRV and decreased LF much more than HF, resulting in a significantly smaller LF/HF ratio. A larger study[118] confirmed that flecainide, also encainide and moricizine, decreased HRV in post-MI patients but found no correlation between the change in HRV and mortality during follow-up. Thus, some antiarrhythmic drugs associated with increased mortality can reduce HRV. However, it is not known whether these changes in HRV have any direct prognostic significance.

Scopolamine and HRV

Low-dose muscarinic receptor blockers, such as atropine and scopolamine, may produce a paradoxical increase in vagal efferent activity, as suggested by a decrease in heart rate. Different studies examined the effects of transdermal scopolamine on indices of vagal activity in patients with a recent MI[119][120][121][122] and with congestive heart failure.[123] Scopolamine markedly increases HRV, which indicates that pharmacological modulation of neural activity with scopolamine may effectively increase vagal activity. However, the efficacy during long-term treatment has not been assessed. Furthermore, low-dose scopolamine does not prevent ventricular fibrillation caused by acute myocardial ischemia in post-MI dogs.[124]

Thrombolysis and HRV

The effect of thrombolysis on HRV (assessed by pNN50) was reported in 95 patients with acute MI.[125] HRV was higher 90 minutes after thrombolysis in the patients with patency of the infarct-related artery. However, this difference was no longer evident when the entire 24 hours were analyzed.

Exercise Training and HRV

Exercise training may decrease cardiovascular mortality and sudden cardiac death.[126] Regular exercise training is also thought capable of modifying the autonomic balance.[127][128] A recent experimental study designed to assess the effects of exercise training on markers of vagal activity has simultaneously provided information on changes in cardiac electrical stability.[129] Conscious dogs documented to be at high risk by the previous occurrence of ventricular fibrillation during acute myocardial ischemia were randomly assigned to 6 weeks of either daily exercise training or cage rest followed by exercise training.[129] After training, HRV (SDNN) increased by 74%, and all animals survived a new ischemic test. Exercise training can also accelerate recovery of the physiological sympathovagal interaction, as shown in post-MI patients.[130]

Clinical Use of HRV

Although HRV has been the subject of numerous clinical studies investigating a wide spectrum of cardiological and noncardiological diseases and clinical conditions, a general consensus of the practical use of HRV in adult medicine has been reached only in two clinical scenarios. Depressed HRV can be used as a predictor of risk after acute MI and as an early warning sign of diabetic neuropathy.

Assessment of Risk After Acute MI

The observation[12] that in patients with an acute MI the absence of respiratory sinus arrhythmias is associated with an increase in “in-hospital” mortality represents the first of a large number of reports[16][93][131] that have demonstrated the prognostic value of assessing HRV to identify high-risk patients.

Depressed HRV is a powerful predictor of mortality and of arrhythmic complications (for example, symptomatic sustained ventricular tachycardia) in patients after acute MI[16][131] (Fig 8). The predictive value of HRV is independent of other factors established for postinfarction risk stratification, such as depressed left ventricular ejection fraction, increased ventricular ectopic activity, and presence of late potentials. For prediction of all-cause mortality, the value of HRV is similar to that of left ventricular ejection fraction. However, HRV is superior to left ventricular ejection fraction in predicting arrhythmic events (sudden cardiac death and ventricular tachycardia).[131] This permits speculation that HRV is a stronger predictor of arrhythmic mortality rather than nonarrhythmic mortality. However, clear differences between HRV in patients suffering from sudden and nonsudden cardiac death after acute MI have not been observed. Nevertheless, this also might be related to the nature of the presently used definition of sudden cardiac death,[132] which is bound to include not only patients suffering arrhythmia-related death but also fatal reinfarctions and other cardiovascular events.

The value of both conventional time domain and frequency domain parameters has been fully assessed in several independent prospective studies. Because of using optimized cutoff values

defining normal and depressed HRV, these studies may slightly overestimate the predictive value of HRV. Nevertheless, the confidence intervals of such cutoff values are rather narrow because of the sizes of investigated populations. Thus, the observed cutoff values of 24-hour measures of HRV, that is, SDNN <50 ms and HRV triangular index <15 for highly depressed HRV, or SDNN <100 ms and HRV triangular index <20 for moderately depressed HRV, are likely to be broadly applicable.

It is not known whether different indices of HRV (assessments of the short- and long-term components) can be combined in a multivariate fashion in order to improve postinfarction risk stratification. There is a general consensus, however, that combination of other measures with the assessment of overall 24-hour HRV is probably redundant.

Pathophysiological Considerations

It has not been established whether depressed HRV is part of the mechanism of increased postinfarction mortality or is merely a marker of poor prognosis. The data suggest that depressed HRV is not a simple reflection of sympathetic overdrive and/or vagal withdrawal due to poor ventricular performance but that it also reflects depressed vagal activity, which has a strong association with the pathogenesis of ventricular arrhythmias and sudden cardiac death.[112]

Assessment of HRV for Risk Stratification After Acute MI

Traditionally, HRV used for risk stratification after MI has been assessed from 24-hour recordings. HRV measured from short-term ECG recordings also provides prognostic information for risk stratification after MI but whether it is as powerful as that from 24-hour recordings is uncertain.[133134135] HRV measured from short-term recordings is depressed in patients at high risk; the predictive value of depressed HRV increases with increased length of recording. Thus, the use of nominal 24-hour recordings may be recommended for risk stratification studies after MI. On the other hand, the assessment of HRV from short-term recordings can be used for initial screening of survivors of acute MI.[136] Such an assessment has similar sensitivity but lower specificity for predicting patients at high risk compared with 24-hour HRV.

Spectral analysis of HRV in survivors of MI suggested that the ULF and VLF components carry the highest predictive value.[93] Because the physiological correlate of these components is unknown and because these components correspond to up to 95% of the total power, which can be easily assessed in the time domain, the use of individual spectral components of HRV for risk stratification after MI is not more powerful than the use of those time domain methods that assess overall HRV.

Development of HRV After Acute MI

The time after acute MI at which the depressed HRV reaches the highest predictive value has not been investigated comprehensively. Nevertheless, the general consensus is that HRV should be assessed shortly before hospital discharge, that is, approximately 1 week after index infarction. Such a recommendation also fits well into the common practice of hospital management of survivors of acute MI.

HRV is decreased early after acute MI and begins to recover within a few weeks; it is maximally but not fully recovered by 6 to 12 months after MI.[91137] Assessment of HRV at both the early stage of MI (2 to 3 days after acute MI)[84] and before discharge from the hospital (1 to 3 weeks after acute MI)

offers important prognostic information. HRV measured late (1 year) after acute MI also predicts further mortality.[138] Data from animal models suggest that the speed of HRV recovery after MI correlates with subsequent risk.[115]

HRV Used for Multivariate Risk Stratification

The predictive value of HRV alone is modest. Combination with other techniques substantially improves the positive predictive accuracy of HRV over a clinically important range of sensitivity (25% to 75%) for cardiac mortality and arrhythmic events (Fig 9).

Improvements of the positive predictive accuracy over the range of sensitivities have been reported for combinations of HRV with mean heart rate, left ventricular ejection fraction, frequency of ventricular ectopic activity, parameters of high resolution ECGs (presence or absence of late potentials), and clinical assessment.[139] However, it is not known which other stratification factors are the most practical and most feasible to be combined with HRV for multifactorial risk stratification.

Systematic multivariate studies of post-MI risk stratification are needed before a consensus can be reached and before it can be recommended how to combine HRV with other variables of proven prognostic importance. Many aspects that are not relevant for a univariate risk stratification need to be examined: It is not obvious whether the optimum cutoff values of individual risk factors known from univariate studies are appropriate in a multivariate setting. Different multivariate combinations are probably needed for optimizing predictive accuracy at different ranges of sensitivity. Stepwise strategies should be examined to identify optimum sequences of performing individual tests used in multivariate stratification.

Summary and Recommendations for Interpreting Predictive Value of Depressed HRV After Acute MI

The following facts should be noted when HRV assessment is exploited in clinical studies and/or trials involving survivors of acute myocardial infarction.

Depressed HRV is a predictor of mortality and arrhythmic complications that is independent of other recognized risk factors.

There is a general consensus that HRV should be measured approximately 1 week after index infarction.

Although HRV assessed from short-term recordings provides prognostic information, HRV measured in nominal 24-hour recordings is a stronger risk predictor. HRV assessed from short-term recordings may be used for initial screening of all survivors of an acute MI.

No currently recognized HRV measure provides better prognostic information than the time domain HRV measures assessing overall HRV (SDNN or HRV triangular index). Some other measures, for example, ULF of entire 24-hour spectral analysis, perform equally well. A high-risk group may be selected by the dichotomy limits of SDNN <50 ms or HRV triangular index <15.

For clinically meaningful ranges of sensitivity, the predictive value of HRV alone is modest, although it is higher than that of any other recognized risk factor. To improve the predictive value, HRV may

be combined with other factors. However, an optimum set of risk factors and corresponding dichotomy limits have not yet been established.

Assessment of Diabetic Neuropathy

As a complication of diabetes mellitus, autonomic neuropathy is characterized by early and widespread neuronal degeneration of small nerve fibers of both sympathetic and parasympathetic tracts.[140] Its clinical manifestations are ubiquitous with functional impairment and include postural hypotension, persistent tachycardia, gustatory sweating, gastroparesis, bladder atony, and nocturnal diarrhea. Once clinical manifestations of diabetic autonomic neuropathy (DAN) supervene, the estimated 5-year mortality is approximately 50%.[141] Thus, early subclinical detection of autonomic dysfunction is important for risk stratification and subsequent management. Analyses of short-term and/or long-term HRV have been proven useful in detecting DAN.[96142143144145146147]

For the patient presenting with a real or suspected DAN, there are three HRV methods from which to choose: (1) simple bedside RR interval methods, (2) long-term time domain measures that are more sensitive and more reproducible than the short-term tests, and (3) frequency domain analysis performed under short-term steady state conditions, which is useful in separating sympathetic from parasympathetic abnormalities.

Long-term Time Domain Measures

HRV computed from 24-hour Holter records are more sensitive than simple bedside tests (Valsava maneuver, orthostatic test, and deep breathing[11]) for detecting DAN. Most experience has been obtained with the NN50[144] and SDSD (see Table 1)[145] methods. When the NN50 count is used, where the lower 95% confidence interval for total counts range from 500 to 2000, depending on the age, about half of diabetic patients demonstrate abnormally low counts per 24 hours. Moreover, there is a strong correlation between the percentage of patients with abnormal counts and the extent of autonomic neuropathy determined from conventional measures.

Besides their increased sensitivity, these 24-hour time domain methods are strongly correlated with other established HRV measurements and have been found to be reproducible and stable over time. Similar to survivors of MI, patients with DAN are also predisposed to poor outcomes such as sudden death, but it remains to be determined whether the HRV measures confer prognostic information among diabetics.

Frequency Domain Measures

The following abnormalities in frequency HRV analysis are associated with DAN: (1) reduced power in all spectral bands, which is the most common finding,[96146147148] (2) failure to increase LF on standing, which is a reflection of impaired sympathetic response or depressed baroreceptor sensitivity,[96147] (3) abnormally reduced total power with unchanged LF/HF ratio,[96] and (4) a leftward shift in the LF central frequency, the physiological meaning of which needs further elucidation.[147]

In advanced neuropathic states, the resting supine power spectrum often reveals extremely low amplitudes of all spectral components, making it difficult to separate signal from noise.[96146147] It is therefore recommended that an intervention such as standing or tilt be included. Another method to

overcome the low signal-to-noise ratio is to introduce a coherence function that utilizes the total power coherent with one or the other frequency band.[146]

Other Clinical Potential

Selected studies investigating HRV in other cardiological diseases are listed in Table 4.[100102104110149150151152153154155156157158159160161162163164165166167]

Future Possibilities

Development of HRV Measurement

The currently available time domain methods predominantly used to assess long-term profile of HRV probably are sufficient for this purpose. Their improvements are possible, especially in terms of numerical robustness. The contemporary nonparametric and parametric spectral methods probably are sufficient to analyze short-term ECGs without transient changes of heart period modulations.

Apart from the need to develop numerically robust techniques suitable for fully automatic measurement (the geometric methods are only one possibility in this direction), the following three areas deserve attention.

Dynamics and Transient Changes of HRV

The present possibilities of characterizing and quantifying the dynamics of the RR interval sequence and transient changes of HRV are sparse and still under mathematical development. Moreover, it is plausible to assume that proper assessment of HRV dynamics will lead to substantial improvement in our understanding of both the modulations of heart period and their physiological and pathophysiological correlates.

It remains to be seen whether the methods of nonlinear dynamics will be most appropriate for the measurement of transient changes of RR intervals or whether new mathematical models and algorithmic concepts will be needed to tailor the principles of measurement more closely to the physiological nature of cardiac periodograms. In any case, the task of assessing transient changes in HRV seems to be more important than further refinements of the current technology used to analyze stable stages of heart period modulations.

PP and PR Intervals

Little is known about the interplay between the PP and PR autonomic modulations. For these reasons, the sequence of PP intervals also should be studied.[168] Unfortunately, a precise location of a P-wave fiducial point is almost impossible to achieve in surface ECGs recorded with the current technology. However, developments in the technology should allow PP interval and PR interval variability to be investigated in future studies.

Multisignal Analysis

The modulations of heart periods are naturally not the only manifestation of the autonomic regulatory mechanisms. Currently, commercial or semicommercial equipment exists that enables simultaneous recording of ECG, respiration, blood pressure, and so forth. However, despite the ease with which the signals can be recorded, no widely accepted method exists for comprehensive

multisignal analysis. Each signal can be analyzed separately, for example, with parametric spectral methods, and the results of the analysis compared. Analysis of coupling between physiological signals allows the properties of the coupling to be measured.[169170171172173174]

Studies Needed to Improve Physiological Understanding

Efforts should be made to find the physiological correlates and the biological relevance of various HRV measures currently used. In some cases, for example, the HF component, this has been achieved. In other cases, for example, the VLF and ULF components, the physiological correlates are still largely unknown.

This uncertain knowledge limits the interpretation of associations between these variables and the risk of cardiac events. The use of markers of autonomic activity is very attractive. However, unless a tenable mechanistic link between these variables and cardiac events is found, there is an inherent danger of concentrating therapeutic efforts on the modification of these markers.[111112] This may lead to incorrect assumptions and serious misinterpretations.

Possibilities of Future Clinical Utility

Normal Standards

Large prospective population studies with longitudinal follow-up are needed to establish normal HRV standards for various age and sex subsets.[110] Recently, investigators from the Framingham Heart Study reported on the time and frequency domain measures of HRV in 736 elderly subjects and the relationship of these HRV measures to all-cause mortality during 4 years of follow-up.[175] These investigators concluded that HRV offers prognostic information independent of and beyond that provided by traditional risk factors. Additional population-based HRV studies involving the full age spectrum in male and female subjects need to be performed.

Physiological Phenomena

It would be of interest to evaluate HRV in various circadian patterns such as normal day-night cycles, sustained reversed day-night cycles (evening-night shift work), and transiently altered day-night cycles such as might occur with international travel. The autonomic fluctuations occurring during various stages of sleep including rapid eye movement (REM) sleep have been studied in only a few subjects. In normal subjects, the HF vagal component of the power spectrum is augmented only during non-REM sleep, whereas in post-MI patients, this increase in HF is absent.[176]

The autonomic nervous system response to athletic training and rehabilitative exercise programs after various disease states is thought to be a conditioning phenomenon. HRV data should be useful in understanding the chronological aspects of training and the time to optimal conditioning as it relates to the autonomic influences on the heart. Also, HRV may provide important information about deconditioning with prolonged bed rest and with weightlessness and zero gravity that accompany space flight.

Pharmacological Responses

Many medications act directly or indirectly on the autonomic nervous system, and HRV can be used to explore the influence of various agents on sympathetic activity and parasympathetic activity. It is

known that parasympathetic blockade with full-dose atropine produces marked diminution of HRV. Low-dose scopolamine has vagotonic influences and is associated with increased HRV, especially in the HF range. β-Adrenergic blockade was observed to increase HRV and to reduce the normalized units of the LF component.[15] Considerably more research is needed to understand the effects and clinical relevance of altered vagotonic and adrenergic tone on total HRV power and its various components in health and disease.

At present, few data exist on the effects of calcium channel blockers, sedatives, anxiolytics, analgesics, anesthetics, antiarrhythmic agents, narcotics, and chemotherapeutic agents such as vincristine and doxorubicin on HRV.

Risk Stratification

Both time and frequency measures of HRV calculated from long 24-hour and short 2- to 15-minute ECG recordings have been used to predict time to death after MI as well as the risk of all-cause mortality and sudden cardiac death in patients with structural heart disease[162163177] and a number of other pathophysiological conditions.[177] With diagnostic instruments that can measure HRV together with the frequency and complexity of ventricular arrhythmias, signal-averaged ECG, ST-segment variability, and repolarization heterogeneity, it should be possible to markedly improve the identification of patients at risk for sudden cardiac death and arrhythmic events. Prospective studies are needed to evaluate the sensitivity, specificity, and predictive accuracy of combined testing.

Fetal and neonatal HRV is an important area of investigation, and it might provide early information about fetal and neonatal distress and identify those at risk for sudden infant death syndrome. Most of the preliminary work in this field was carried out in the early 1980s before the more sophisticated power spectral techniques became available. Insight into autonomic maturation in the developing fetus also might be possible through the proper application of these techniques.

Disease Mechanisms

A fertile area of research is the use of HRV techniques to explore the role of autonomic nervous system alterations in disease mechanisms, especially those conditions in which sympathovagal factors are thought to play an important role. Recent work suggests that alterations in autonomic innervation to the developing heart might be responsible for some forms of long QT syndrome.[178] Fetal HRV studies in pregnant mothers with this disorder is certainly feasible and might be very informative.[179]

The role of the autonomic nervous system in essential hypertension is an important area of investigation.[180] The question regarding the primary or secondary role of enhanced sympathetic activity in essential hypertension might be answered by longitudinal studies of subjects who are initially normotensive. Does essential hypertension result from augmented sympathetic activity with altered responsiveness of neural regulatory mechanisms?

Several primary neurological disorders including Parkinson’s disease, multiple sclerosis, Guillain-Barre syndrome, and orthostatic hypotension of the Shy-Drager type are associated with altered autonomic function. In some of these disorders, changes in HRV may be an early manifestation of the condition and may be useful in quantitating the rate of disease progression and/or the efficacy of therapeutic interventions. This same approach may also be useful in the evaluation of secondary

autonomic neurological disorders that accompany diabetes mellitus, alcoholism, and spinal cord injuries.

Conclusions

HRV has considerable potential to assess the role of autonomic nervous system fluctuations in normal healthy individuals and in patients with various cardiovascular and noncardiovascular disorders. HRV studies should enhance our understanding of physiological phenomena, the actions of medications, and disease mechanisms. Large prospective longitudinal studies are needed to determine the sensitivity, specificity, and predictive value of HRV in the identification of individuals at risk for subsequent morbid and mortal events.

Appendix A

Normal Values of Standard Measures of HRV

As no comprehensive investigations of all HRV indices in large normal populations have yet been performed, some of the normal values listed in the following table were obtained from studies involving small numbers of subjects. The values should therefore be considered as approximate and no definite clinical conclusions should be based on them. The adjustment of normal limits for age, sex, and environment, which is also needed, has been omitted here because of the limited sources of data.

Table 5 lists only values of those measures of HRV that might be suggested for standardization of further physiological and clinical studies.[181]

Appendix B

Suggestion of Procedures for Testing of Commercial Equipment Designed to Measure HRV

Concept

To achieve comparable accuracy of measurements reported by different commercial equipment, each device should be tested independently of the manufacturer (for example, by an academic institution). Each test should involve several short-term and, if applicable, long-term test recordings with precisely known HRV parameters and with different morphological characteristics of the ECG signal. If the involvement of the manufacturer is required during the testing procedure (for example, for manual editing of the labels of QRS complexes), the manufacturer must be blinded in respect of both the true HRV parameters of the testing recordings and the features used to obtain the signal. In particular, when the results of the test are disclosed to the manufacturer for further improvement of the device or otherwise, new tests should involve a completely new set of test recordings.

Technical Requirements

Each device should be tested comprehensively, including all its parts. In particular, the test should involve both the recording and the analytical part of the device. An appropriate technology should be used to record a fully reproducible signal with precisely known HRV parameters, that is, the test signal should be computer and/or hardware generated. Both brand new recorders as well as

recorders that have been routinely used and routinely serviced for approximately half of their lifetime should be used in the tests if this is feasible (the testing should not be delayed for newly introduced systems). If a manufacturer claims that the device is capable of analyzing ECG records (such as Holter tapes) obtained with recorders of other manufacturers, each combination should be tested independently.

Since the analysis of HRV by implantable devices may be foreseen, similar procedures as described further should be used to generate simulated intracardiac signals. If feasible, implantable devices with fully charged batteries as well as devices with partly discharged batteries should be tested.

Test Recordings

It is intrinsically difficult to know precisely the HRV parameters of any real ECG recordings independently of equipment used to analyze the recording. Therefore, simulated ECG signals are preferable. However, the morphology of such simulated ECG signals as well as the HRV characteristics must closely reflect the morphology of real recordings. The discrete frequency used to generate such signals must be substantially higher than the sampling frequency of the tested device. Features that should be introduced into such recordings should include different factors known to influence or potentially influence the precision of HRV assessment, for example, variable noise levels, variable morphology of QRS signals that may cause jitter of the fiducial point, randomly alternating noise in different channels of the signal, gradual and abrupt changes of HRV characteristics, and different frequencies of atrial and ventricular ectopic beats with realistic morphologies of the signal.

The quality of records on magnetic tape–based systems may not be constant during long-term recording due to spool torque control, back tension, and other factors. Performance of all recorders can be influenced by changes of the outside environment. Long-term (full 24-hour test) rather than short-term tests therefore should be used.

Testing Procedures

Each device or each configuration of the device should be tested with several different recordings having different mixtures of features and different HRV characteristics. For each test record and for each selected portion of the test record, the HRV parameters obtained from the commercial device should be compared with the known characteristics of the initial signal. Any discrepancies found should be itemized in respect to features introduced into the recording, for example, errors caused by increased noise, errors caused by fiducial point wander, and so forth. Systematic bias introduced by the equipment as well as its relative errors should be established.

Reporting the Results

A technical report of the testing should be prepared solely at the testing site independent of the manufacturer(s) of the tested device.

Appendix C

The Task Force was established by the Board of the European Society of Cardiology and cosponsored by the North American Society of Pacing and Electrophysiology. It was organized jointly by the Working Groups on Arrhythmias and on Computers of Cardiology of the European

Society of Cardiology. After exchanges of written views on the subject, the main meeting of a writing core of the Task Force took place May 8 through 10, 1994, on Necker Island, British Virgin Islands. After external reviews, the text of this report was approved by the Board of the European Society of Cardiology on August 19, 1995, and by the Board of the North American Society of Pacing and Electrophysiology on October 3, 1995.

Members of the Task Force

The Task Force was composed of 17 members: Cochairmen: A. John Camm, London, UK; Marek Malik, London, UK; Members: J. Thomas Bigger, Jr, New York, NY; Günter Breithardt, Münster, Germany; Sergio Cerutti, Milano, Italy; Richard J. Cohen, Cambridge, Mass; Philippe Coumel, Paris, France; Ernest L. Fallen, Hamilton, Canada; Harold L. Kennedy, St Louis, Mo; Robert E. Kleiger, St Louis, Mo; Federico Lombardi, Milano, Italy; Alberto Malliani, Milano, Italy; Arthur J. Moss, Rochester, NY; Jeffrey N. Rottman, St Louis, Mo; Georg Schmidt, München, Germany; Peter J. Schwartz, Pavia, Italy; and Donald H. Singer, Chicago, Ill.

While the text of this report was contributed to and approved by all members of the Task Force, the structure of the text was designed by the Writing Committee of the Task Force, composed of the following members: Marek Malik (Chairman), J. Thomas Bigger, A. John Camm, Robert E. Kleiger, Alberto Malliani, Arthur J. Moss, and Peter J. Schwartz.

Selected Abbreviations and Acronyms

HF	=	high frequency
HRV	=	heart rate variability
LF	=	low frequency
MI	=	myocardial infarction
ULF	=	ultra low frequency
VLF	=	very low frequency

1Membership of the Task Force is listed in “Appendix C.”

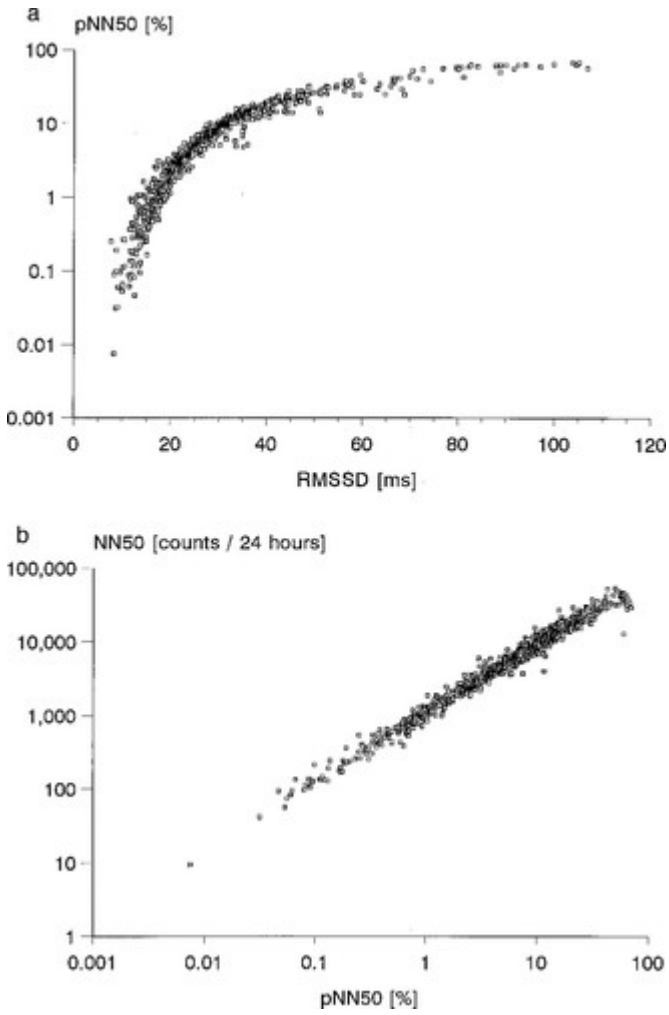

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Figure 1. Relationship between the RMSSD and pNN50 (a) and pNN50 and NN50 (b) measures of HRV assessed from 857 nominal 24-hour Holter tapes recorded in survivors of acute myocardial infarction before hospital discharge. The NN50 measure used in b was normalized in respect to the length of the recording (data of St George's Post-infarction Research Survey Programme). Also see Table 1.

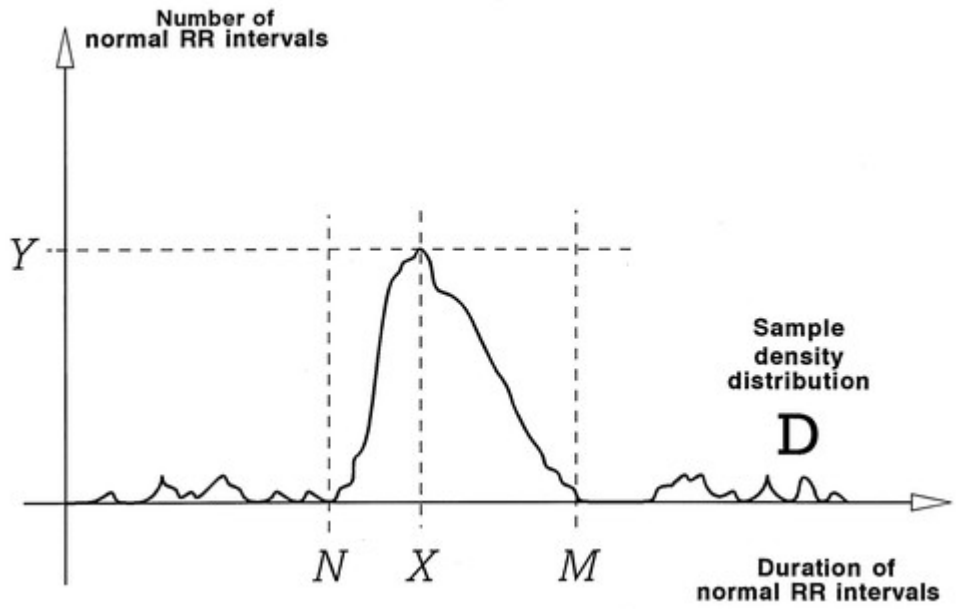

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Figure 2. To perform geometric measures on the NN interval histogram, the sample density distribution D is constructed, which assigns the number of equally long NN intervals to each value of their lengths. The most frequent NN interval length *X* is established, that is, *Y*=D(*X*) is the maximum of the sample density distribution D. The HRV triangular index is the value obtained by dividing the area integral of D by the maximum *Y*. When the distribution D with a discrete scale is constructed on the horizontal axis, the value is obtained according to the formula HRV index=(total number of all NN intervals)/*Y*. For the computation of the TINN measure, the values *N* and *M* are established on the time axis and a multilinear function q constructed such that q(t)=0 for t≤*N* and t≥*M* and q(*X*)=*Y*, and such that the integral $\int_0^{+\infty}$ (D(t) −q(t))^2 dt is the minimum among all selections of all values *N* and *M*. The TINN measure is expressed in milliseconds and given by the formula TINN=*M*−*N*. Also see Table 1.

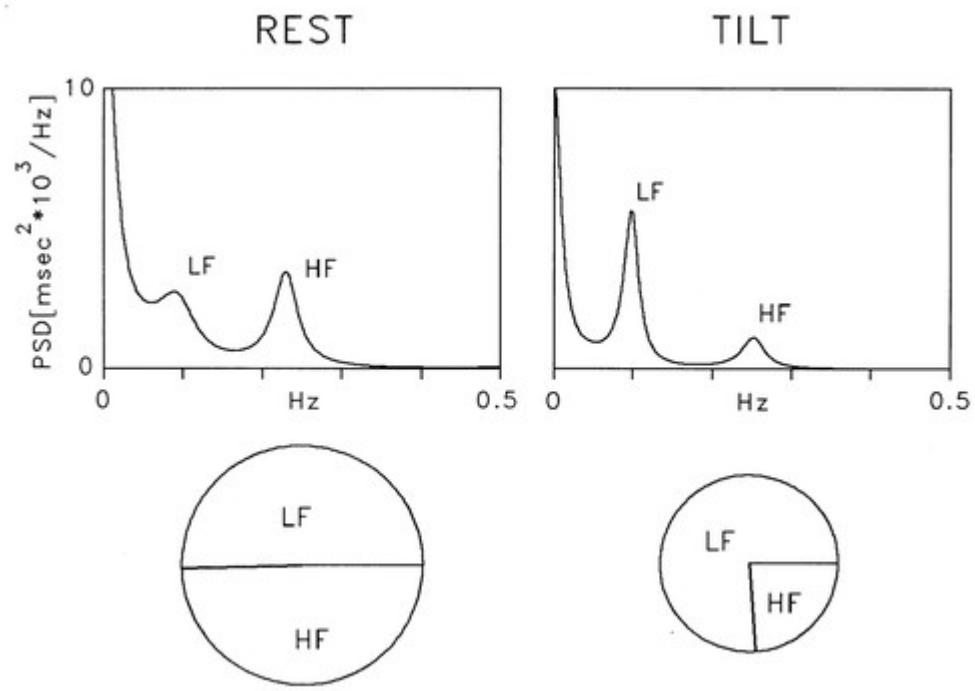

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Figure 3. Spectral analysis (autoregressive model, order 12) of RR interval variability in a healthy subject at rest and during 90° head-up tilt. At rest, two major components of similar power are detectable at low and high frequencies. During tilt, the LF component becomes dominant, but as total variance is reduced, the absolute power of LF appears unchanged compared with rest. Normalization procedure leads to predominant LF and smaller HF components, which express the alteration of spectral components due to tilt. Pie charts show the relative distribution together with the absolute power of the two components represented by the area. During rest, the total variance of the spectrum was 1201 ms^2, and its VLF, LF, and HF components were 586 ms^2, 310 ms^2, and 302 ms^2, respectively. Expressed in normalized units (nu), the LF and HF were 48.95 and 47.78 nu, respectively. The LF/HF ratio was 1.02. During tilt, the total variance was 671 ms^2, and its VLF, LF, and HF components were 265 ms^2, 308 ms^2, and 95 ms^2, respectively. The LF and HF were 75.96 and 23.48 nu, respectively. The LF/HF ratio was 3.34. Thus, note that for instance, the absolute power of the LF component was slightly decreased during tilt while the normalized units of LF were substantially increased.

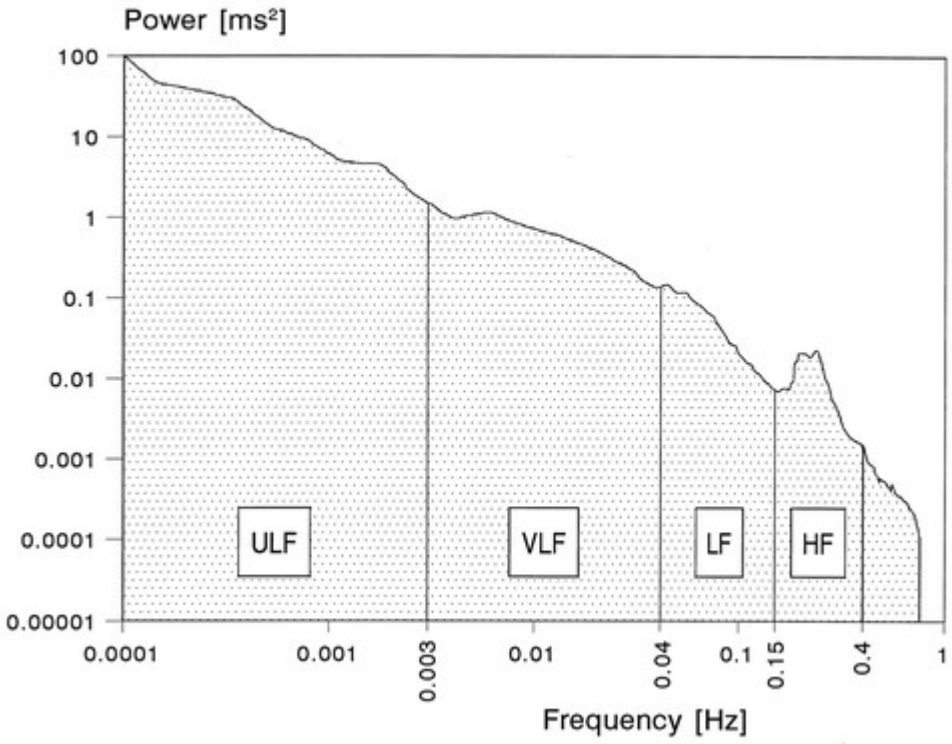

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Figure 4. Example of an estimate of power spectral density obtained from the entire 24-hour interval of a long-term Holter recording. Only the LF and HF components correspond to peaks of the spectrum, while the VLF and ULF can be approximated by a line in this plot with logarithmic scales on both axes. The slope of such a line is the α measure of HRV.

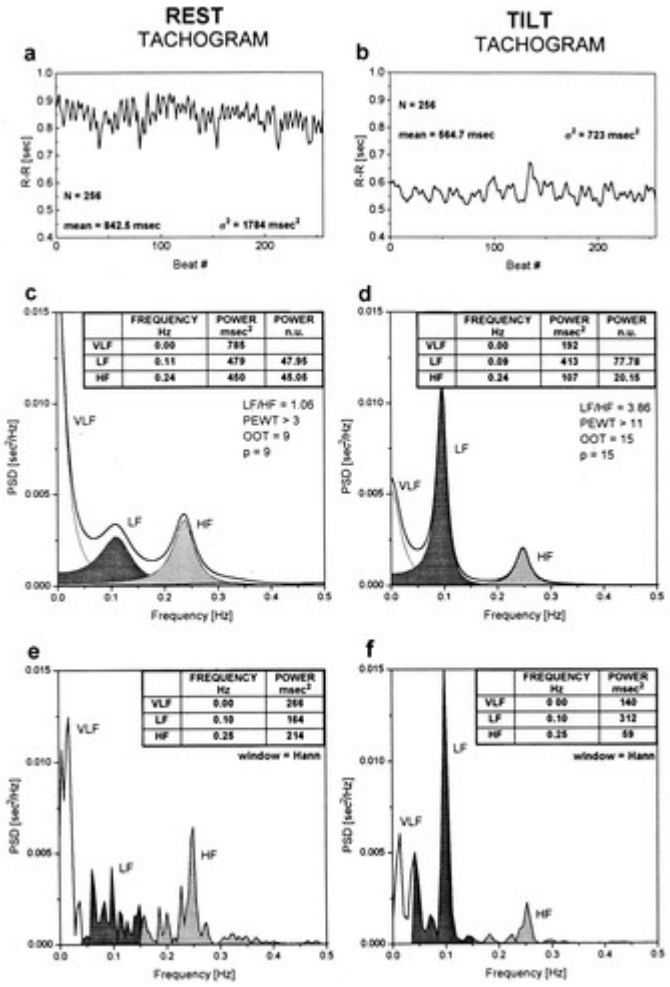

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Figure 5. Interval tachogram of 256 consecutive RR values in a normal subject at supine rest (a) and after head-up tilt (b). The HRV spectra are shown, calculated by parametric autoregressive modeling (c and d) and by a fast Fourier transform–based nonparametric algorithm (e and f). Mean values (m), variances (s^2), and the number (N) of samples are indicated. For c and d, VLF, LF, and HF central frequency, power in absolute value and power in normalized units (n.u.) are also indicated together with the order p of the chosen model and minimal values of the prediction error whiteness test (PEWT) and optimal order test (OOT) that satisfy the tests. In e and f, the peak frequency and the power of VLF, LF, and HF were calculated by integrating the power spectral density (PSD) in the defined frequency bands. The window type is also specified. In c through f, the LF component is indicated by dark shaded areas and the HF component by light shaded areas.

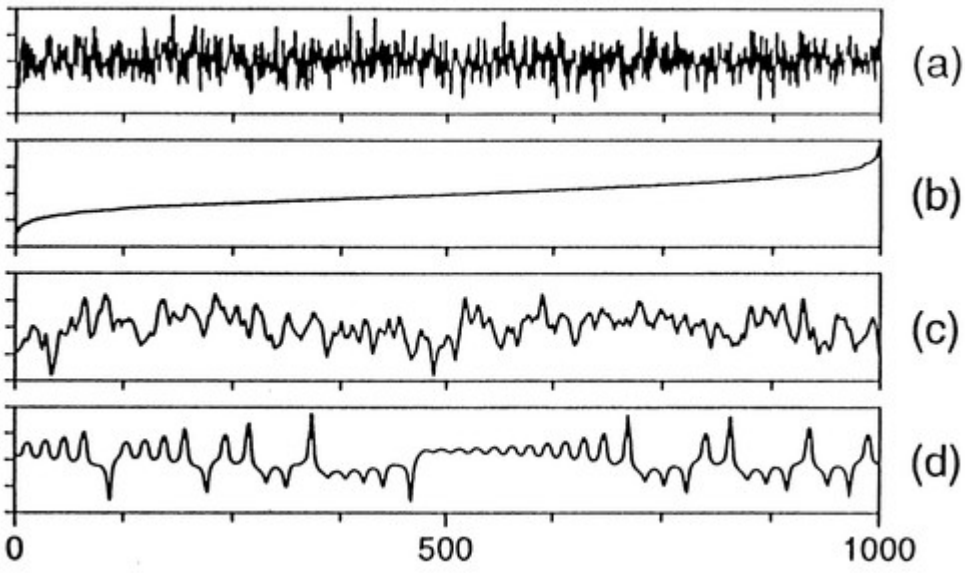

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Figure 6. Example of four synthesized time series with identical means, standard deviations, and ranges. Series (c) and (d) also have identical autocorrelation functions and therefore identical power spectra. Reprinted with permission.[39]

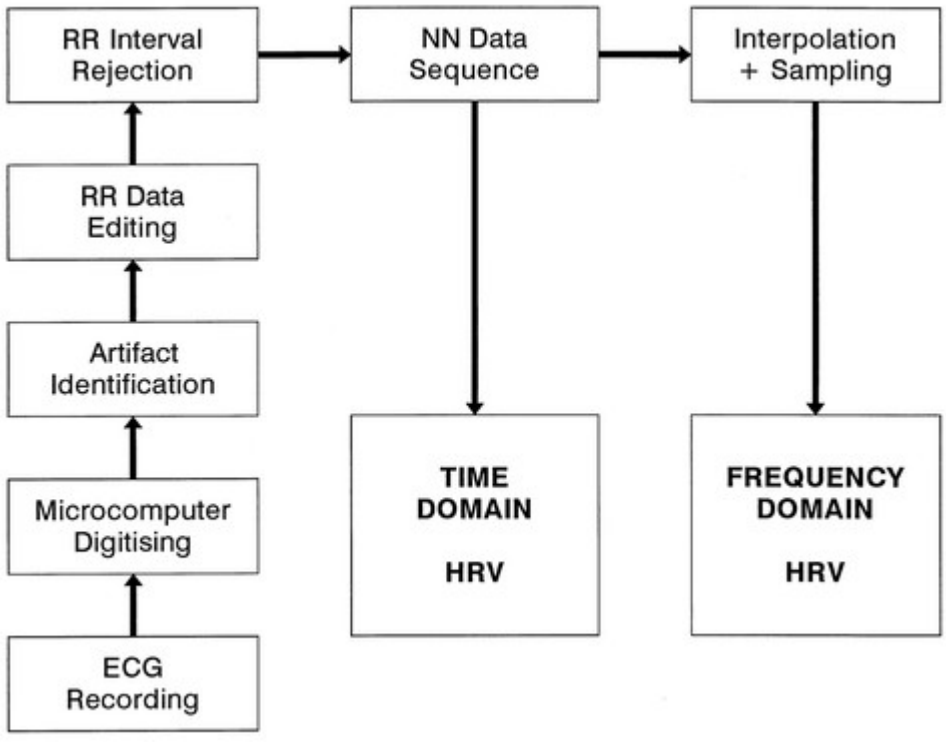

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Figure 7. Flow chart summarizing individual steps used when recording and processing the ECG signal in order to obtain data for HRV analysis.

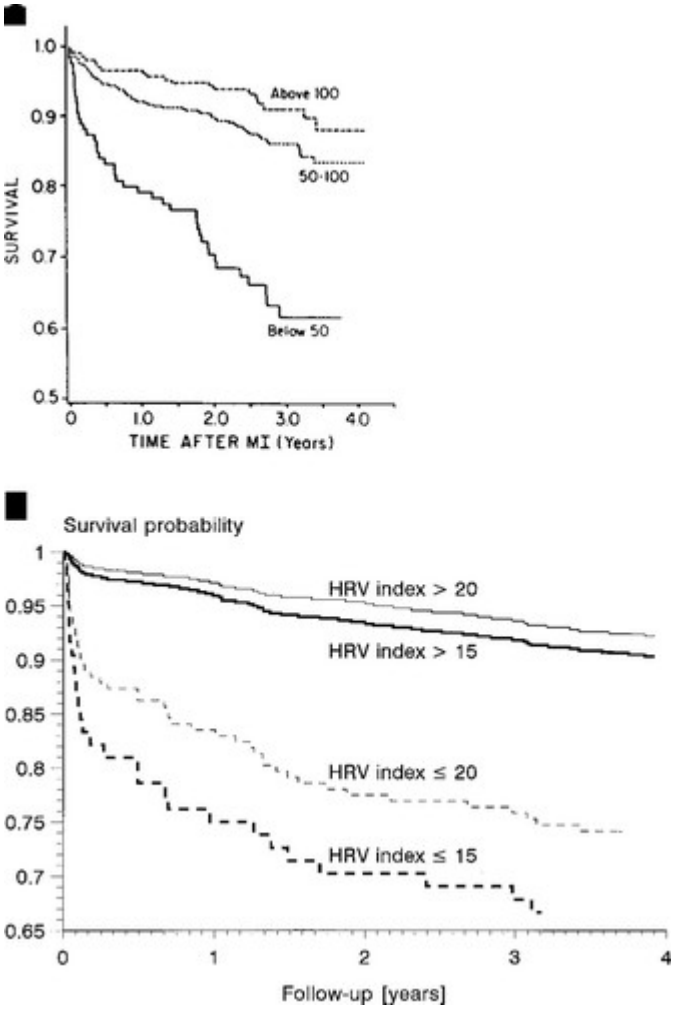

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Figure 8. Cumulative survival of patients after MI. a, Survival of patients stratified according to 24-hour SDNN values into three groups with cutoff points of 50 and 100 ms (reprinted with permission[16]). b, Similar survival curves of patients stratified according to 24-hour HRV triangular index values with cutoff points of 15 and 20 units, respectively (data of St George's Post-infarction Research Survey Programme). Also see Table 1.

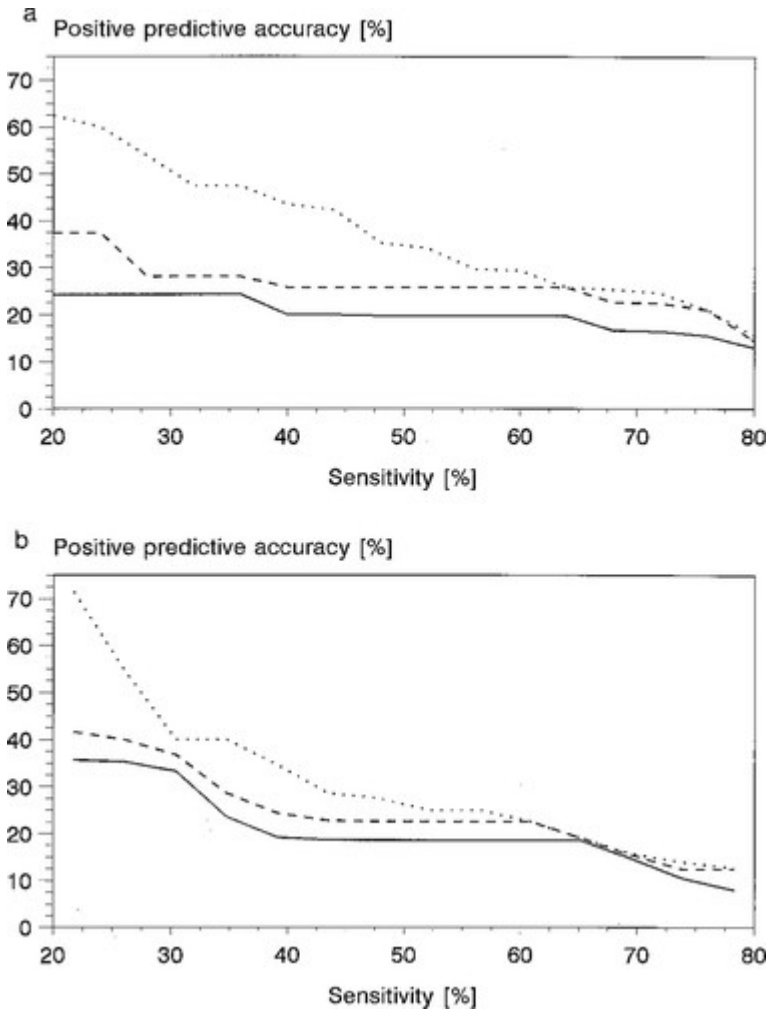

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Figure 9. Comparison of positive predictive characteristics of HRV (solid lines) and of combinations of HRV with left ventricular ejection fraction (dashed lines) and of HRV with left ventricular ejection fraction and ectopic counts on 24-hour ECGs (dotted lines) used for identification of patients at risk of 1-year cardiac mortality (a) and 1-year arrhythmic events (sudden death and/or symptomatic sustained ventricular tachycardia, b) after acute myocardial infarction (data of St George's Post-infarction Research Survey Programme).

Table 1. Selected Time Domain Measures of HRV

Variable	Units	Description
Statistical Measures		
SDNN	ms	Standard deviation of all NN intervals

Variable	Units	Description
SDANN	ms	Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording
SDSD	ms	Standard deviation of differences between adjacent NN intervals
NN50 count		Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer
pNN50	%	NN50 count divided by the total number of all NN intervals
Geometric Measures		
HRV triangular index		Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms (1/128 seconds) (details in Fig 2)
TINN	ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals (details in Fig 2)
Differential index	ms	Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights (eg, at the levels of 1000 and 10 000 samples)[20]
Logarithmic index		Coefficient φ of the negative exponential curve $k \cdot e^{-\varphi t}$, which is the best approximation of the histogram of absolute differences between adjacent NN intervals[21]

Table 2. Selected Frequency Domain Measures of HRV

Variable	Units	Description	Frequency Range
Analysis of Short-term Recordings (5 min)			

Variable	Units	Description	Frequency Range
5-min total power	ms^2	The variance of NN intervals over the temporal segment	≈≤0.4 Hz
VLF	ms^2	Power in VLF range	≤0.04 Hz
LF	ms^2	Power in LF range	0.04-0.15 Hz
LF norm	nu	LF power in normalized units LF/(total power−VLF)×100	
HF	ms^2	Power in HF range	0.15-0.4 Hz
HF norm	nu	HF power in normalized units HF/(total power−VLF)×100	
LF/HF		Ratio LF [ms^2]/HF[ms^2]	
Analysis of Entire 24 Hours			
Total power	ms^2	Variance of all NN intervals	≈≤0.4 Hz
ULF	ms^2	Power in the ULF range	≤0.003 Hz
VLF	ms^2	Power in the VLF range	0.003-0.04 Hz
LF	ms^2	Power in the LF range	0.04-0.15 Hz
HF	ms^2	Power in the HF range	0.15-0.4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	≈≤0.04 Hz

Table 3. Approximate Correspondence of Time Domain and Frequency Domain Methods Applied to 24-Hour ECG Recordings

Time Domain Variable	Approximate Frequency Domain Correlate
SDNN	Total power

Time Domain Variable	Approximate Frequency Domain Correlate
HRV triangular index	Total power
TINN	Total power
SDANN	ULF
SDNN index	Mean of 5-minute total power
RMSSD	HF
SDSD	HF
NN50 count	HF
pNN50	HF
Differential index	HF
Logarithmic index	HF

See Table 1 for explanation of time domain variables.

Table 4. Summary of Selected Studies Investigating Clinical Value of HRV in Cardiological Diseases Other Than Myocardial Infarction

Disease State	Author of Study	Population (No. of Patients)	Investigation Parameter	Clinical Finding	Potential Value
Hypertension	Guzzetti et al, 1991[149]	49 hypertensive 30 normals	Spectral AR	⇑LF found in hypertensives compared with normals with blunting of circadian patterns	Hypertension is characterized by a depressed circadian rhythmicity of LF

Disease State	Author of Study	Population (No. of Patients)	Investigation Parameter	Clinical Finding	Potential Value
	Langewitz et al, 1994[150]	41 borderline hypertensive 34 hypertensive 54 normals	Spectral FFT	Reduced parasympathetic in hypertensive patients	Support the use of nonpathological therapy of hypertension that ⇑ vagal tone (eg, exercise)
CHF	Saul et al, 1988[151]	25 chronic CHF NYHA III,IV 21 normals	Spectral Blackman-Tukey 15-min acquisition	⇓Spectral power all frequencies, especially >0.04 Hz in CHF patients	In CHF, there is ⇓ vagal but relatively preserved sympathetic modulation of HR
	Casolo et al, 1989[102]	20 CHF NYHA II,III,IV 20 normals	Time domain RR interval histogram with 24-h Holter	Low HRV	Reduced vagal activity in CHF patients
	Binkley et al, 1991[152]	10 dilated cardiomyopathy (EF 14% to 40%) 10 normals	Spectral FFT 4-min supine acquisition	⇓HF power (>0.1 Hz) in CHF ⇑LF/HF	Withdrawal of parasympathetic tone observed in CHF. CHF has imbalance of autonomic tone with ⇓ parasympathetic and a predominance of sympathetic tone
	Kienzle et al, 1992[104]	23 CHF NYHA II,III,IV	Spectral FFT Time domain 24-48-h Holter	Alterations of HRV not tightly linked to severity of CHF ⇓HRV was related to sympathetic excitation	

Disease State	Author of Study	Population (No. of Patients)	Investigation Parameter	Clinical Finding	Potential Value
	Townend et al, 1992[153]	12 CHF NYHA III,IV	Time domain 24-h Holter	HRV⇑ during ACE inhibitor treatment	
	Binkley et al, 1993[154]	13 CHF NYHA II,III	Spectral FFT 4-min supine acquisition	12 weeks of ACE inhibitor treatment ⇑HF HRV	Significant augmentation of parasympathetic tone was associated with ACE inhibitor therapy
	Woo et al, 1994[155]	21 CHF NYHA III	Poincaré plots Time domain 24-h Holter	Complex plots are associated with ⇑norepinephrine levels and greater sympathetic activation	Poincaré plots may assist analysis of sympathetic influences
Heart transplantation	Alexopoulos et al, 1988[156]	19 transplant 10 normals	Time domain 24-h Holter	Reduced HRV in denervated donor hearts; recipient innervated hearts had more HRV	
	Sands et al, 1989[100]	17 transplant 6 normals	Spectral FFT 15-min supine acquisition	HRV from 0.02 to 1.0 Hz; 90% reduced	Patients with rejection documented biopsy show significantly more variability
Chronic mitral regurgitation	Stein et al, 1993[157]	38 chronic mitral regurgitation	Spectral FFT Time domain 24-h Holter	HR and measures of ULF by SDANN correlated with ventricular performance and predicted clinical events	May be prognostic indicator of atrial fibrillation, mortality, and progression to valve surgery

Disease State	Author of Study	Population (No. of Patients)	Investigation Parameter	Clinical Finding	Potential Value
Mitral valve prolapse	Marangoni et al, 1993[158]	39 female mitral valve prolapse 24 female controls	Spectral AR 10-min supine acquisition	MVP patients had ⇓HF	MVP patients had low vagal tone
Cardiomyopathies	Counihan et al, 1993[159]	104 HCM	Spectral FFT Time domain 24-h Holter	Global and specific vagal tone measurements of HRV were ⇓ in symptomatic patients	HRV does not add to the predictive accuracy of known risk factors in HCM
SD or CA	Dougherty et al, 1992[160]	16 CA survivors 5 CA nonsurvivors 5 normals	Spectral AR Time domain 24-h Holter	HRV as measured by LF power and SDNN were significantly related to 1-y mortality	HRV is clinically useful to risk stratify CA survivors for 1-y mortality
	Huikuri et al, 1992[161]	22 CA survivors 22 control	Spectral AR Time domain 24-h Holter	⇓HF power in CA survivors; LF power did not discriminate CA survivors Circadian pattern of HRV found in all patients	
	Algra et al, 1993[110]	193 SD cases 230 symptomatic patients	Time domain 24-h Holter	⇓Short-term variation (0.05-0.50 Hz) independently increased the risk of SD by a factor of 2.6 ⇓Long-term variation (0.02-0.05 Hz) increased the risk of SD by a factor of 2	HRV may be used to estimate the risk of SD

ACE indicates angiotensin-converting enzyme; AR, autoregressive; CA, cardiac arrest; CAD, coronary artery disease; CHF, congestive heart failure; EF, ejection fraction; FFT, fast Fourier transform; HCM, hypertrophic cardiomyopathy; HF, high frequency; HRV heart rate variability; LF, low frequency; MVP, mitral valve prolapse; NYHA, New York Heart Association classification; SD, sudden death; SVT, supraventricular tachycardia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 5. Normal Values of Standard Measures of HRV

Variable	Units	Normal Values (mean±SD)
Time Domain Analysis of Nominal 24 hours[181]		
SDNN	ms	141±39
SDANN	ms	127±35
RMSSD	ms	27±12
HRV triangular index		37±15
Spectral Analysis of Stationary Supine 5-min Recording		
Total power	ms^2	3466 ±1018
LF	ms^2	1170±416
HF	ms^2	975±203
LF	nu	54±4
HF	nu	29±3
LF/HF ratio		1.5-2.0

See Table 1 also.

Table 4A. Continued

Disease State	Author of Study	Population (No. of Patients)	Investigation Parameter	Clinical Finding	Potential Value
	Myers et al, 1986[162]	6 normals 12 patients with structural heart disease (6 with and 6 without SD)	Time and frequency domain 24-h Holter	Both time and frequency domain indices separated normals from SD patients ⇓HF power (0.35-0.5 Hz) was the best separator between heart disease patients with and without SD	HF power may be a useful predictor of SD
	Martin et al, 1986[163]	20 normals 5 patients experiencing SD during Holter monitoring	Time domain 24-h Holter	SDNN index significantly lower in SD patients	Time domain indices may identify increased risk of SD
Ventricular arrhythmias	Vybiral et al, 1993[164]	24 VF 19 CAD	Time domain 24-h Holter	HRV indices do not change consistently before VF	
	Huikuri et al, 1993[165]	18 VT or CA	Spectral AR 24-h Holter	All power spectra of HRV were significantly ⇓ before the onset of sustained VT than before nonsustained VT	A temporal relation exists between the decrease of HRV and the onset of sustained VT
	Hohnloser et al, 1994[166]	14 post-MI with VF or sustained 14 post-MI (matched)	Spectral FFT Time domain 24-h Holter	HRV of post MI-CA survivors do not differ from other post MI patients; they differ strikingly in terms of baroreflex sensitivity	Baroreflex sensitivity, not HRV, distinguished post-MI patients with and without VF and VT
Supraventricular arrhythmias	Kocovic et al, 1993[167]	64 SVT	Spectral FFT Time domain 5-min supine acquisition 24-h Holter	⇑HR, ⇓HRV, and ⇓parasympathetic components after radiofrequency ablation	Parasympathetic ganglia and fibers may be more dense in the mid and anterior low septum

Footnotes

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