Guidelines

Heart rate variability

Standards of measurement, physiological interpretation, and clinical use

Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (Membership of the Task Force listed in the Appendix)

Introduction

The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death[1–4]. Experimental evidence for an association between a propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has encouraged the development of quantitative markers of autonomic activity.

Heart rate variability (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 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: standardize nomenclature and develop definitions of terms; specify standard methods of measurement; define physiological and pathophysiological correlates; describe currently appropriate clinical applications, and identify areas for future research.

In order 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, rather, 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 heart beats 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. In order 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 analysed 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 heart rate variability 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 the heart rate itself. Twenty years ago, Sayers and others focused attention on the existence of physiological rhythms imbedded in the beat-to-beat heart rate signal[7–10].

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 post-infarction mortality with reduced HRV was first shown by Wolf *et al.* in 1977[12]. In 1981, Akselrod *et al.* introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control[13].

These frequency–domain analyses contributed to the understanding of the autonomic background of RR interval fluctuations in the heart rate record[14,15]. The clinical importance of HRV became apparent in the late 1980s when it was confirmed that HRV was a strong and independent predictor of mortality following an acute myocardial infarction[16–18]. With the availability of new, digital, high frequency, 24-h multi-channel electrocardiographic recorders, HRV has the potential to provide additional valuable insight into physiological and pathological conditions and to enhance risk stratification.

Measurement of heart rate variability

Time domain methods

Variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. With these methods either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous electrocardiographic (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, etc. Other time–domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, Valsalva manoeuvre, or secondary to 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 h, more complex *statistical time-domain measures* can be calculated. These may be divided into two classes, (a) those derived from direct measurements of the NN intervals or instantaneous heart rate, and (b) those derived from the differences between NN intervals. These variables may be derived from analysis of the total electrocardiographic 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, e.g. rest, sleep, etc.

The simplest variable to calculate is the *standard deviation of the NN interval* (SDNN), i.e. 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-h period and thus encompasses both short-term high frequency variations, as well as the lowest frequency components seen in a 24-h period. As the period of monitoring decreases, SDNN estimates shorter and shorter cycle lengths. It should also be noted that the total variance of HRV increases with the length of analysed 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. Thus, in practice, it is inappropriate to compare SDNN measures obtained from recordings of different durations. However, 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-min recordings and nominal 24 h long-term recordings seem 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 interval calculated over short periods, usually 5 min, which is an estimate of the changes in heart rate due to cycles longer than 5 min, and the *SDNN index*, the mean of the 5-min standard deviation of the NN interval calculated over 24 h, which measures the variability due to cycles shorter than 5 min.

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 these measurements of short-term variation estimate high frequency variations in heart rate and thus are highly correlated (Fig. 1).

Geometrical methods
The series of NN intervals can also 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, etc., and a simple formula is used which judges the variability based on the geometric and/or graphic properties of the resulting pattern. Three general approaches are used in geometric methods: (a) a basic measurement of the geometric pattern (e.g. the width of the distribution histogram at the specified level) is converted into the measure of HRV, (b) the geometric pattern is interpolated by a mathematically defined shape (e.g. 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 (c) the geometric shape is classified into several
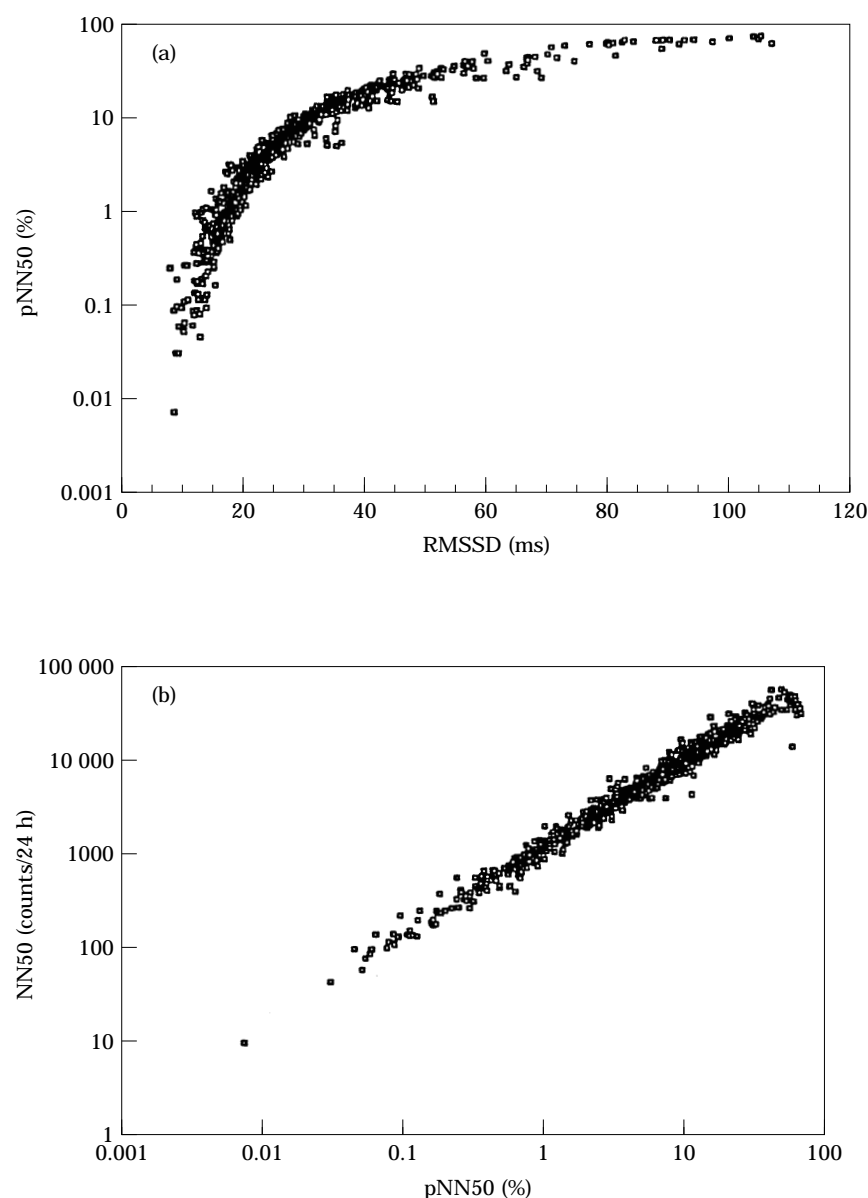
Figure 1 **Relationship between the RMSSD and pNN50 (a), and pNN50 and NN50 (b) measures of HRV assessed from 857 nominal 24-h Holter tapes recorded in survivors of acute myocardial infarction prior to hospital discharge. The NN50 measure used in panel (b) was normalized in respect to the length of the recording (Data of St. George's Post-infarction Research Survey Programme.)**

pattern-based categories which represent different classes of HRV (e.g. 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 which is not too fine or too coarse and which permits the construction of smoothed histograms. Most experience has been obtained with bins approximately 8 ms long (precisely 7·8125 ms = 1/128 s) which corresponds to the precision of current commercial equipment.

The *HRV triangular index* measurement is the integral of the density distribution (i.e. 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, i.e. 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 to the most frequent sampling of 128 Hz, the size of the bins should be quoted. The *triangular interpolation of NN*
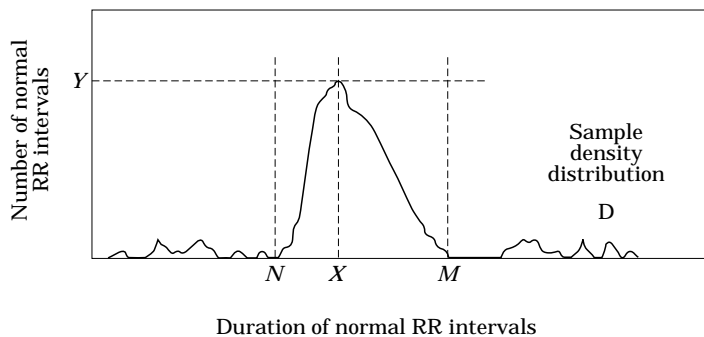
Duration of normal RR intervals

Figure 2 **To perform geometrical 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 constructing the distribution** D **with a discrete scale 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** $t \leq N$ **and** $t \geq M$ **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 ms and given by the formula** **TINN** $= M - N$.

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 the HRV triangular index and TINN are shown in Fig. 2. Both these measures express overall HRV measured over 24 h 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.

The major advantage of geometric methods lies in their relative insensitivity to the analytical quality of the series of NN intervals[20]. The major disadvantage is the need for a reasonable number of NN intervals to construct the geometric pattern. In practice, recordings of at least 20 min (but preferably 24 h) should be used to ensure the correct performance of the geometric methods, i.e. 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 are recommended for time–domain HRV assessment: SDNN (estimate of overall HRV); HRV triangular index (estimate of overall HRV); SDANN (estimate of long-term components of HRV), and RMSSD (estimate of short-term components of HRV). Two estimates of the overall HRV are recommended because the HRV triangular index permits only casual pre-processing 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 method selected should correspond to the aim of each study. Methods that might be recommended for clinical practices are summarized in the Section entitled Clinical use of heart rate variability.

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 the Section on 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

Table 1   Selected time-domain measures of HRV

Variable	Units	Description
		Statistical measures
SDNN	ms	Standard deviation of all NN intervals.
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min 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 min 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 s). (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 (e.g. at the levels of 1000 and 10 000 samples)[21].
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[22].

spectral density (PSD) analysis provides the basic information of how power (i.e. variance) distributes as a function of frequency. Independent of the method employed, only an estimate of the true PSD of the signals can be obtained by proper mathematical algorithms.

Methods for the calculation of PSD may be generally classified as *non-parametric* and *parametric*. In most instances, both methods provide comparable results. The advantages of the non-parametric methods are: (a) the simplicity of the algorithm employed (Fast Fourier Transform — FFT — in most of the cases) and (b) the high processing speed, whilst the advantages of parametric methods are: (a) smoother spectral components which can be distinguished independently of pre-selected frequency bands, (b) easy post-processing of the spectrum with an automatic calculation of low and high frequency power components and easy identification of the central frequency of each component, and (c) 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 to verify the suitability of the chosen model and its complexity (i.e. 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 min[7,10,13,15,24]: very low frequency (VLF), low frequency (LF), and high frequency (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

the 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 non-harmonic component which does not have coherent properties and which 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 (e.g. ≤5 min) is a dubious measure and should be avoided when interpreting the PSD of short-term ECGs.

Measurement of VLF, LF and HF power components is usually made in absolute values of power (ms²), but LF and HF may also be measured in normalized units (n.u.)[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 n.u. emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system. Moreover, normalization tends to minimize the effect on the values of LF and HF components of the changes in total power (Fig. 3). Nevertheless, n.u. should always be quoted with absolute values of LF and HF power in order to describe in total the distribution of power in spectral components.

Long-term recordings Spectral analysis may also be used to analyse the sequence of NN intervals in the entire 24-h period. The result then includes an ultra-low frequency component (ULF), in addition to VLF, LF and HF components. The slope of the 24-h spectrum can also be assessed on a log–log scale by linear fitting the spectral values. Table 2 lists selected frequency–domain measures.
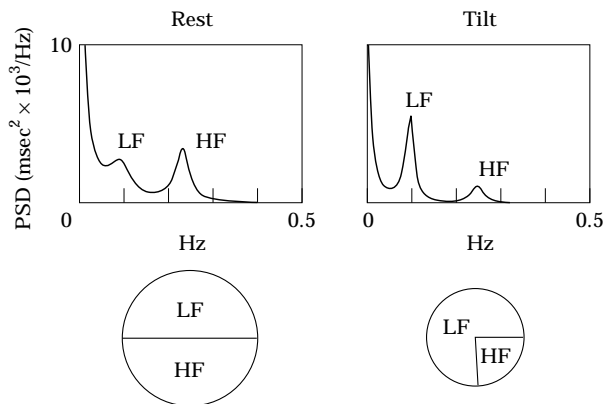
Figure 3 Spectral analysis (autoregressive model, order 12) of RR interval variability in a healthy subject at rest and during 90° head-up tilt. At rest, two major components of similar power are detectable at low and high frequencies. During tilt, the LF component becomes dominant but, as total variance is reduced, the absolute power of LF appears unchanged compared to rest. Normalization procedure leads to predominant LF and smaller HF components, which express the alteration of spectral components due to tilt. The 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, the LF and HF were 48·95 n.u. and 47·78 n.u., 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. Expressed in normalized units, the LF and HF were 75·96 n.u. and 23·48 n.u., 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 whilst the normalized units of LF were substantially increased

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, 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-h period[25]. Thus, spectral analysis performed in the entire 24-h period as well as spectral results obtained from shorter segments (e.g. 5 min) averaged over the entire 24-h 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 detailed information about autonomic modulation of RR intervals available in shorter recordings[25]. It should be remembered that the components of HRV provide measurements of the degree of autonomic modulations rather
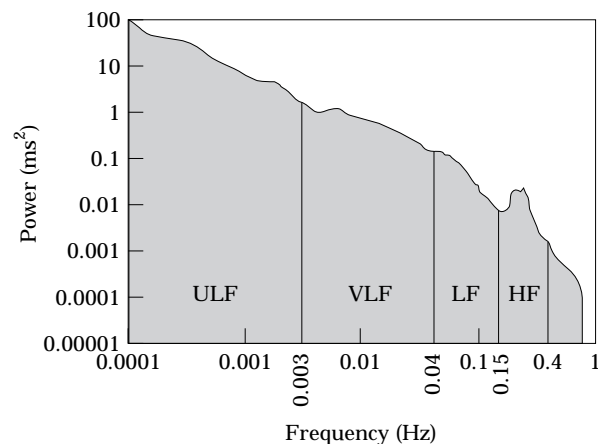

Figure 4 Example of an estimate of power spectral density obtained from the entire 24-h interval of a long-term Holter recording. Only the LF and HF components correspond to peaks of the spectrum while the VLF and ULF can be approximated by a line in this plot with logarithmic scales on both axes. The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

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- and long-term electrocardiograms should always be strictly distinguished, as reported in Table 2.

The analysed 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.

In order 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 analysed by specific methods which currently constitute a challenging research topic, but which 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 employed[29].

The sampling rate has to 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 250–500 Mz or perhaps even higher[30], while a lower sampling rate (in any case ≥ 100 Hz) may behave satisfactorily only if an algorithm of interpolation (e.g. parabolic) is used to refine the R wave fiducial point[31,32].

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 behaviour of the regression algorithm and to verify that the spectral components of interest are not significantly affected.

Table 2   Selected frequency domain measures of HRV

Variable	Units	Description	Frequency range
		Analysis of short-term recordings (5 min)	
5 min total power	ms^2	The variance of NN intervals over the temporal segment	approximately ≤ 0.4 Hz
VLF	ms^2	Power in very low frequency range	≤ 0.04 Hz
LF	ms^2	Power in low frequency range	0.04–0.15 Hz
LF norm	n.u.	LF power in normalised units LF/(Total Power–VLF) × 100	
HF	ms^2	Power in high frequency range	0.15–0.4 Hz
HF norm	n.u.	HF power in normalised units HF/(Total Power–VLF) × 100	
LF/HF		Ratio LF [ms^2]/HF [ms^2]	
		Analysis of entire 24 h	
Total power	ms^2	Variance of all NN intervals	approximately ≤ 0.4 Hz
ULF	ms^2	Power in the ultra low frequency range	≤ 0.003 Hz
VLF	ms^2	Power in the very low frequency range	0.003–0.04 Hz
LF	ms^2	Power in the low frequency range	0.04–0.15 Hz
HF	ms^2	Power in the high frequency range	0.15–0.4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	approximately ≤ 0.04 Hz

The choice of QRS fiducial point may be critical. It is necessary to use a well tested algorithm (i.e. derivative+threshold, template, correlation method, etc.) in order 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 signals or on its autocorrelation function may reduce this error. Preferentially, short-term recordings which 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 which 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_i-R_{i-1} interval vs 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 vs 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 recognised 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. In order to standardize the methods, the use of the RR interval tachogram with the parametric method, or the regularly sampled interpolation of DES with the non-parametric method may be suggested; nevertheless, regularly sampled interpolation of DES is also suitable for parametric methods. The sampling frequency of interpolation of DES has to be sufficiently high that the Nyquist frequency of the spectrum is not within the frequency range of interest.

Standards for non-parametric methods (based upon 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 employed (Hann, Hamming, and triangular windows are most frequently used)[36]. The method of calculating the power in respect of the window should also be quoted. In addition to requirements described in other parts of this document, each study employing the non-parametric spectral analysis of HRV should quote all these parameters.

Standards for parametric methods should 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 have to be calculated in order to test the reliability of the model. The prediction
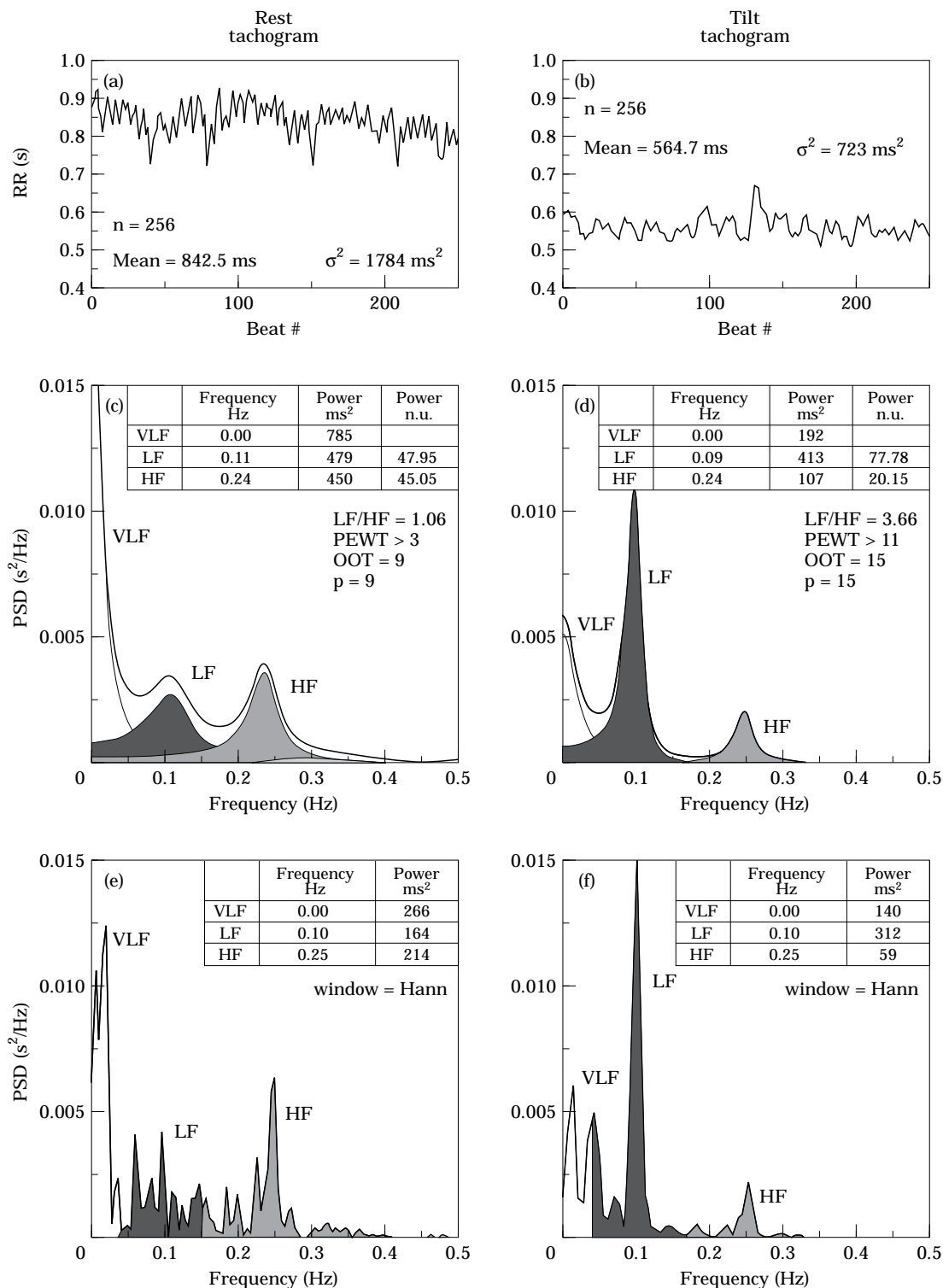
Rest
tachogram

Tilt
tachogram

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 modelling (c and d), and by a FFT based non-parametric 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 PEWT and OOT which satisfy the tests. In (e) and (f), the peak frequency and the power of VLF, LF and HF were calculated by integrating the PSD in the defined frequency bands. The window type is also specified. In panels (c) to (f), the LF component is indicated by dark shaded areas and the HF component by light shaded areas.**

Table 3 Approximate correspondence of time domain and frequency domain methods applied to 24-h ECG recordings

Time domain variable	Approximate frequency domain correlate
SDNN	Total power
HRV triangular index	Total power
TINN	Total power
SDANN	ULF
SDNN index	Mean of 5 min total power
RMSSD	HF
SDSD	HF
NN50 count	HF
pNN50	HF
Differential index	HF
Logarithmic index	HF

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 which 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 8–20, fulfilling the PEWT test and complying with the OOT test (p ≈ min(OOT)).

Correlation and differences between time and frequency domain measures
When analysing stationary short-term recordings, more experience and theoretical knowledge exists on the physiological interpretation of the frequency–domain measures compared to the time–domain measures derived from the same recordings.

However, many time- and frequency-domain variables measured over the entire 24-h 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 h is difficult, for the reasons mentioned (section entitled Long-term recordings). Thus, unless special investigations are performed which use the 24-h HRV signal to extract information other than the usual frequency components (e.g. the log–log slope of spectrogram), the results of frequency–domain analysis are equivalent to those of 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 analysed by these techniques may give identical results. Trends of decreasing or increasing cycle length are in reality not symmetrical[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 (d, Fig. 6) 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
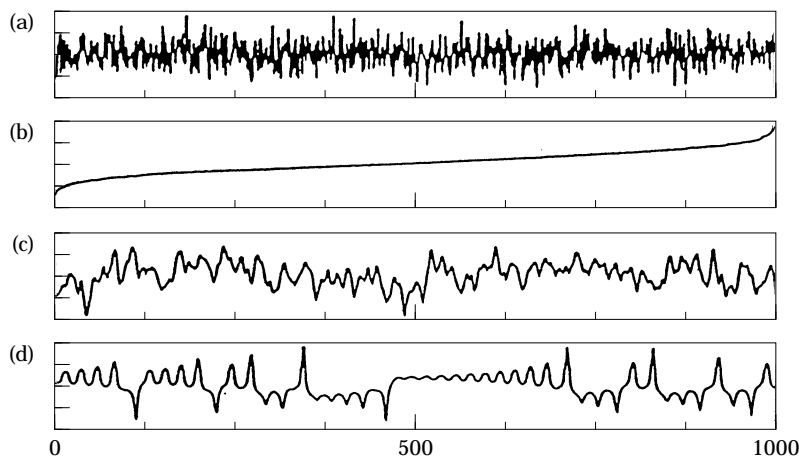

Figure 6 **Example of four synthesised time series with identical means, standard deviations, and ranges. Series (c) and (d) also have identical autocorrelation functions and therefore identical power spectra. Reprinted with permission[39].**

(e.g. blood pressure). The spectrum of counts is preferable if RR intervals are related to a continuous signal (e.g. respiration), or to the occurrence of special events (e.g. 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 accelerating 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.

Non-linear methods

Non-linear phenomena are certainly involved in the genesis of HRV. They are determined by complex interactions of haemodynamic, electrophysiological and humoral variables, as well as by autonomic and central nervous regulations. It has been speculated that analysis of HRV based on the methods of non-linear dynamics might elicit valuable information for the physiological interpretation of HRV and for the assessment of the risk of sudden death. The parameters which have been used to measure non-linear 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, Poincarè 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 employed[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 bio-medical data including HRV analysis. It is possible that integral complexity measures are not adequate to analyse biological systems and thus, are too insensitive to detect the non-linear 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, e.g. the scaling index method[50,51]. However, no systematic study has been conducted to investigate large patient populations using these methods.

At present, the non-linear methods represent potentially promising tools for HRV assessment, but standards are lacking and the full scope of these methods cannot be assessed. Advances in technology and the interpretation of the results of non-linear 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, transient coronary occlusion, etc. 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-h ambulatory monitoring. Nonetheless, the same amount of data available suggest great stability of HRV measures derived from 24-h ambulatory monitoring in both normal subjects[52,53] and in the post-infarction[54] and ventricular arrhythmia[55] populations. There also exists some fragmentary data to suggest that stability of HRV measures may persist for months and years. Because 24-h indices seem to be stable and free of placebo effect, they may be ideal variables with which to assess intervention therapies.

Recording requirements

ECG signal

The fiducial point recognised on the ECG tracing which 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. In order to localize the fiducial point, voluntary standards for diagnostic ECG equipment are satisfactory in terms of signal/noise ratio, common mode rejection, bandwidth, etc.[56] An upper-band frequency cut-off 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 which 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 using solid-state storage recorders, data compression techniques have to be carefully considered in terms of both the effective sampling rate and the

quality of reconstruction methods which 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 investigating short-term recordings. 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 min is needed to assess the HF components of HRV while approximately 2 min are needed to address the LF component. In order to standardize different studies investigating short-term HRV, 5 min 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 (e.g. over 20 min) 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 more easily interpretable results 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 analysed by the time–domain methods should contain at least 18 h of analysable ECG data that includes the whole night.

Little is known about the effects of the environment (e.g. type and nature of physical activity and of 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 should also 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 should also 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 using the statistical time–domain and/or frequency–domain methods, 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' which exclude some intervals from the original RR sequence (e.g. those differing by more than 20% from the previous interval) should not replace manual editing as they are known to behave unsatisfactorily and to have undesirable effects leading potentially to errors[58].

Suggestions for standardisation of commercial equipment
Standard measurement of HRV Commercial equipment designed to analyse short-term HRV should incorporate non-parametric and preferably also parametric spectral analysis. In order 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. Non-parametric spectral analysis should employ at least 512 but preferably 1024 points for 5 min recordings.

Equipment designed to analyse 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 min segments (using the same precision as with the analysis of short-term ECGs). When performing the spectral analysis of the total nominal 24-h record in order 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, e.g. 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 In order 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. As 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 (e.g. computer simulated) of known HRV properties rather than with existing
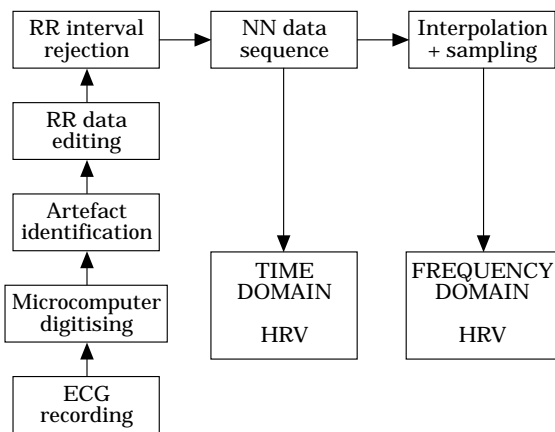
Figure 7 **Flow chart summarizing individual steps used when recording and processing the ECG signal in order to obtain data for HRV analysis.**

databases of already digitized ECGs. When employing commercial equipment 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

In order 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/noise ratio, common mode rejection, bandwidth, etc.

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 the Section on Standard Measurement of HRV and its performance should be independently tested.

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

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

When using statistical time–domain or frequency–domain methods, 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 (e.g. exclusion of

RR intervals according to a certain prematurity threshold) should not be relied on when ensuring the quality of the RR interval sequence.

Physiological correlates of heart rate variability

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[60–62]. Acetylcholine also inhibits the hyperpolarization-activated 'pacemaker' current If[63,64]. 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[65,66]. Conversely, the 'If activation' hypothesis[67] suggest that following 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 cyclic AMP mediated phosphorilation of membrane proteins and increases in ICaL[68] and in If[69,70]. 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. As the sinus node is rich in acetylcholinesterase, the effect of any vagal impulse is brief because the acetylcholine is rapidly hydrolysed. Parasympathetic influences exceed sympathetic effects probably via two independent mechanisms: a cholinergically induced reduction of norepinephrine released in response to sympathetic activity, and 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[73,74]. 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

which can be modulated by central (e.g. vasomotor and respiratory centres) and peripheral (e.g. oscillation in arterial pressure and respiratory movements) oscillators[24]. These oscillators generate rhythmic fluctuations in efferent neural discharge which 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 manoeuvres such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy[13,14,24]. More controversial is the interpretation of the LF component which is considered by some[24,78–80] as a marker of sympathetic modulation (especially when expressing it in normalized units) and by others[13,81] 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 (ms^2), 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. Due to 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-h recordings[24–25] 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-h period is used or when spectra of subsequent shorter segments are averaged. In long-term recordings, the HF and LF components account for 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[24,79]. Conversely, an increase in HF is induced by controlled respiration, cold stimulation of the face and rotational stimuli[24,78].

Summary and recommendations for interpretation of HRV components

Vagal activity is the major contributor to the HF component.

Disagreement exists in respect of the LF component. Some studies suggest that LF, when expressed in normalized units, is a quantitative marker for sympathetic modulations, other studies view LF as reflecting both sympathetic and vagal activity. Consequently, the LF/HF ratio is considered by some investigators to mirror sympatho/vagal balance or to reflect 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 a saturatingly high level of sympathetic input leads to diminished HRV[28].

Changes of HRV related to specific pathologies

A reduction of HRV has been reported in several cardiological and non-cardiological diseases[24,78,81,83].

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-h 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 cardio-cardiac sympatho-sympathetic[86,87] and sympatho-vagal reflexes[75] and suggests that the changes in the geometry of a beating heart due to necrotic and non-contracting segments may abnormally increase the firing of sympathetic afferent fibres by mechanical distortion of the sensory ending[76,87,88]. This sympathetic excitation attenuates the activity of vagal fibres 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[82,85].

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-h recordings analysed over multiple 5 min periods[90,91]. These changes may indicate a shift of sympatho-vagal balance towards sympathetic predominance and reduced vagal tone. Similar conclusions were obtained by considering the changes in the LF/HF ratio. The presence of an alteration in neural control mechanisms was also reflected by the blunting of the day–night variations of the RR interval[91] and LF and HF spectral components [91,92] 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 advanced cardiac failure or after cardiac transplant, and are likely to reflect either 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 fibres, 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[94–97]. 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 analysed in normalized units, no significant difference in comparison to normals was present. Thus, the initial manifestation of this neuropathy is likely to involve both efferent limbs of the autonomic nervous system[96,98].

Cardiac transplantation

A very reduced HRV with no definite spectral components was reported in patients with a recent heart transplant[97,99,100]. The appearance of discrete spectral components in a few patients is considered to reflect cardiac re-innervation[101]. This re-innervation may occur as early as 1 to 2 years post 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 indicates that a non-neural mechanism may also contribute to generate 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 consistently observed in patients with cardiac failure[24,78,81,102–106]. In this condition characterized by signs of sympathetic activation,

such as faster heart rates and high levels of circulating cathecolamines, a relationship between changes in HRV and the extent of left ventricular dysfunction was controversially reported[102,104]. 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, a LF component could not be detected despite clinical signs of sympathetic activation. Thus, in conditions characterized by 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 with which to evaluate the contribution of supraspinal mechanisms in determining the sympathetic activity responsible for low frequency 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 can also 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 multiple observations indicating that cardiac mortality is higher among 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 contains also 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 yet known how much vagal activity (or its markers) has to increase in order to provide adequate protection.

Beta-adrenergic blockade and HRV

The data on the effect of β-blockers on HRV in post-MI patients are surprisingly scanty[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, prior to MI, β-blockade increases HRV only in the animals destined to be at low risk for lethal arrhythmias post-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, and 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[119–122] 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, efficacy during long-term treatment has not been assessed. Furthermore, low dose scopolamine does not prevent ventricular fibrillation due to acute myocardial ischaemia 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 min after thrombolysis in the patients with patency of the infarct-related artery. However, this difference was no longer evident when the entire 24 h were analysed.

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 ischaemia, 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 ischaemic test. Exercise training can also accelerate recovery of the physiological sympatho-vagal interaction, as shown in post-MI patients[130].

Clinical use of heart rate variability

Although HRV has been the subject of numerous clinical studies investigating a wide spectrum of cardiological and non-cardiological 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 myocardial infarction

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] which 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 (e.g. symptomatic sustained ventricular tachycardia) in patients following acute MI[16,131] (Fig. 8). The predictive value of HRV is independent of other factors established for post-infarction 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, but 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 non-arrhythmic mortality. However, clear differences between HRV in patients suffering from sudden and non-sudden cardiac death after acute MI have not been observed. Nevertheless, this might also be related to the nature of the presently used definition of sudden cardiac death[132], which is bound to include not only patients suffering from arrhythmia-related death but also fatal reinfarctions and other cardiovascular events.

The value of both conventional time–domain and frequency–domain parameters have been fully assessed in several independent prospective studies, but because of using optimized cut-off values defining normal and depressed HRV, these studies may slightly
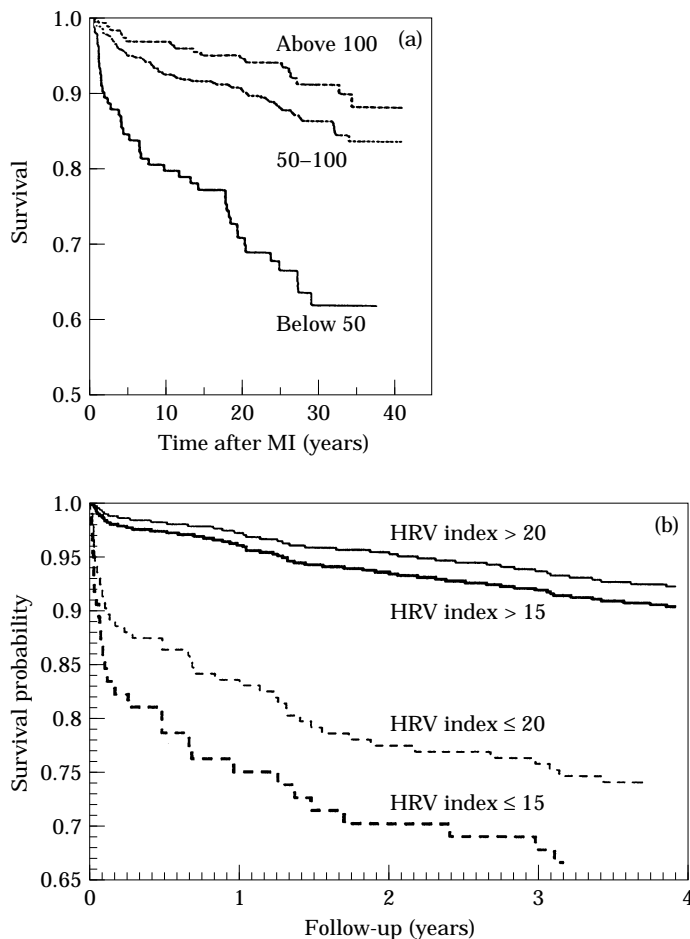
Figure 8 **Cumulative survival of patients after MI. (a) Shows survival of patients stratified according to 24-h SDNN values in three groups with cut-off points of 50 and 100 ms. (Reprinted with permission[16]. (b) Shows similar survival curves of patients stratified according to 24-h HRV triangular index values with cut-off points of 15 and 20 units, respectively. (Data of St. George's Post-infarction Research Survey Programme.)**

overestimate the predictive value of HRV. Nevertheless, the confidence intervals of such cut-off values are rather narrow because of the sizes of the investigated populations. Thus, the observed cut-off values of 24-h measures of HRV, e.g. 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 (e.g. assessments of the short- and long-term components) can be combined in a multivariate fashion in order to improve post-infarction risk stratification. There is a general consensus, however, that combination of other measures with the assessment of overall 24-h HRV is probably redundant.

Pathophysiological considerations
It has not been established whether depressed HRV is part of the mechanism of increased post-infarction mor-

tality or is merely a marker of poor prognosis. The data suggest that depressed HRV is not a simple reflection of the 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 myocardial infarction
Traditionally, HRV used for risk stratification after MI has been assessed from 24-h recordings. HRV measured from short-term electrocardiogram recordings also provides prognostic information for risk stratification following MI but whether it is as powerful as that from 24-h recordings is uncertain[133–135]. HRV measured from short-term recordings is depressed in patients at high risk; the predictive value of depressed HRV increases with increasing the length of recording. Thus, the
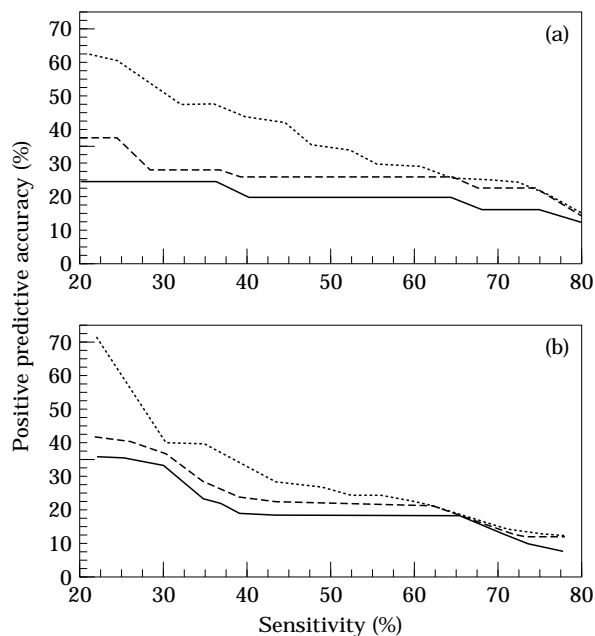
Figure 9 **Comparison of positive predictive characteristics of HRV (solid lines) and of combinations of HRV with left ventricular ejection fraction (dashed lines) and of HRV with left ventricular ejection fraction and ectopic counts on 24-h ECGs (dotted lines) used for identification of patients at 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.)**

use of nominal 24-h 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 to 24-h HRV.

Spectral analysis of HRV in survivors of MI suggested that the ULF and VLF components carry the highest predictive value[93]. As the physiological correlate of these components is unknown and as 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 which assess overall HRV.

Development of HRV after acute myocardial infarction
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 prior to hospital discharge, i.e. approximately 1 week after index infarction. Such a recommendation also fits well into the common practice of hospital management of survivors of acute MI.

Heart rate variability 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[91,137]. Assessment of heart rate variability at both the early stage of MI (2 to 3 days after acute MI)[84] and pre-discharge from hospital (1 to 3 weeks after acute MI) offers important prognostic information. Heart rate variability 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 heart rate variability alone is modest, but combination with other techniques substantially improves its positive predictive accuracy over a clinically important range of sensitivity (25% to 75%) for cardiac mortality and arrhythmic events (Fig. 9).

Improvements in 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 electro-cardiograms (e.g. 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 a combination of HRV with other variables of proven prognostic importance can be recommended. Many aspects that are not relevant for univariate risk stratification need to be examined: it is not obvious whether the optimum cut-off 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 myocardial infarction
The following facts should be noted when exploiting HRV assessment in clinical studies and/or trials involving survivors of acute myocardial infarction.

Depressed HRV is a predictor of mortality and arrhythmic complications independent of other recognised 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-h 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 recognised HRV measure provides better prognostic information than the time–domain HRV measures assessing overall HRV (e.g. SDNN or HRV triangular index). Other measures, e.g. ULF of entire 24-h 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 so far recognised risk factor. To improve the predictive value, HRV may be combined with other factors. However, 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 fibres 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 diarrhoea. 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 proven useful in detecting DAN[96,142–147].

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

Long-term time domain measures
HRV computed from 24-h Holter records are more sensitive than simple bedside tests (e.g. Valsava manoeuvre, 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. Using the NN50 count, where the lower 95% confidence interval for total counts range from 500 to 2000 depending on the age, about half of diabetic patients will demonstrate abnormally low counts per 24 h. 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-h 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: (a) reduced power in all spectral bands which is the most common finding[96,146–148], (b) failure to increase LF on standing, which is a reflection of impaired sympathetic response or depressed baroreceptor sensitivity[96,147]; (c) abnormally reduced total power with unchanged LF/HF ratio[96], and (d) 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[96,146,147]. 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 which 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.

Future possibilities

Development of HRV measurement

The currently available time–domain methods predominantly used to assess the long-term profile of HRV are probably sufficient for this purpose. Improvements are possible, especially in terms of numerical robustness. The contemporary non-parametric and parametric spectral methods are probably sufficient to analyse 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 geometrical 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 the quantifying the dynamics of the RR interval sequence and transient changes of HRV are sparse and still under mathematical development. However, it may be assumed that proper assessment of HRV dynamics will lead to substantial improvements in our understanding of both the modulations of heart period and their physiological and pathophysiological correlates.

Table 4   Summary of selected studies investigating the 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 1991[149]	49 hypertensive 30 normals	Spectral AR	↑ LF found in hypertensives as compared to normals with blunting of circadian patters	Hypertension is characterized by a depressed circadian rhythmicity of LF
	Langewitz 1994[150]	41 borderline hypertensive 34 hypertensive 54 normals	Spectral FFT	Reduced parasympathetic in hypertensive patients	Support the use of non-pathological therapy of hypertension that ↑ vagal tone (e.g. exercise)
Congestive heart failure	Saul 1988[155]	25 chronic CHF NYHA III, IV 21 normals	Spectral Blackman–Turkey 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 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 1991[152]	10 dilated cardiomyopathy (EF 14 to 40%) 10 normals	Spectral FFT 4 min supine acquisition	↓ m high frequency 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 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	
	Townend 1992[153]	12 CHF NYHA III, IV	Time domain 24 h-Holter	HRV ↑ during ACE inhibitor treatment	
	Binkley 1993[154]	13 CHF NYHA II, III	Spectral FFT 4 min supine acquisition	12 weeks of ACE inhibitor treatment ↑ high frequency HRV	A significant augmentation of parasympathetic tone was associated with ACE inhibitor therapy
	Woo 1994[155]	21 CHF NYHA III	Poincarè plots Time-domain 24 h-Holter	Complex plots are associated with ↑ norepinephrine levels and greater sympathetic activation	Poincarè plots may assist analysis of sympathetic influences
Heart transplantation	Alexopoulos 1988[156]	19 transplant 10 normals	Time–domain 24 h-Holter	Reduced HRV in denervated donor hearts; recipient innervated hearts had more HRV	
	Sands 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 1993[157]	38 chronic mitral regurgitation	Spectral FFT Time-domain 24 h-Holter	HR and measures of ultralow frequency by SDANN correlated with ventricular performance and predicted clinical events	May be prognostic indicator of atrial fibrillation, mortality, and progression to valve surgery
Mitral valve prolapse	Marangoni 1993[158]	39 female mitral valve prolapse 24 female controls	Spectral AR 10 min supine acquisition	MVP patients had ↓ high frequency	MVP patients had low vagal tone

Continued

Table 4 Continued.

Disease state	Author of study	Population (no. of patients)	Investigation parameter	Clinical finding	Potential value
Cardiomyopathies	Counihan 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
Sudden death or cardiac arrest	Dougherty 1992[160]	16 CA survivors 5 CA nonsurvivors 5 normals	Spectral AR Time-domain 24 h-Holter	HRV as measured by low frequency power and SDNN were significantly related to 1 year mortality	HRV is clinically useful to risk stratify CA survivors for 1 year mortality
	Huikuri 1992[161]	22 CA survivors 22 control	Spectral AR Time-domain 24 h-Holter	↓ High frequency power in CA survivors — low frequency power did not discriminate CA survivors Circadian pattern of HRV found in all patients	
	Algra 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 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
	Myers 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 1988[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 1993[164]	24 VF 19 CAD	Time-domain 24 h-Holter	HRV indices do not change consistently before VF	
	Huikuri 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 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 term of baroreflex sensitivity	Baroreflex sensitivity, not HRV, distinguished post MI patients with and without VF and VT
Supraventricular arrhythmias	Kocovic 1993[167]	64 SVT	Spectral FFT Time-domain acquisition 24 h-Holter	↑ HR, ↓ HRV and ↓ parasympathetic components after radiofrequency ablation	Parasympathetic ganglia and fibres may be more dense in the mid and anterior low septum

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; NYHA=New York Heart Association classification; SD=sudden death; SVT=supraventricular tachycardia; VF=ventricular fibrillation; VT=ventricular tachycardia.

It remains to be seen whether the methods of non-linear dynamics will be appropriate for the measurement of transient changes in 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 analyse stable stages of heart period modulations.

PP and RR intervals
Little is known about the interplay between the PP and PR autonomic modulations. For these reasons, the sequence of PP intervals should also be studied[168]. Unfortunately, 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 investigate in future studies.

Multisignal analysis
The modulations of heart periods are naturally not the only manifestation of the autonomic regulatory mechanisms. Currently, commercial or semi-commercial equipment exists which enables simultaneous recording of ECG, respiration, blood pressure, etc. However, in spite of the ease with which the signals can be recorded, no widely accepted method exists for comprehensive multisignal analysis. Each signal can be analysed separately, e.g. with parametric spectral methods, and the results of the analysis compared. Analysis of coupling between physiological signals allow the properties of the coupling to be measured[169–174].

Studies needed to improve physiological understanding

Efforts should be made to find the physiological correlates and the biological relevance of various HRV measures currently employed. In some cases, e.g. the HF component, this has been achieved. In other cases, e.g. 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[111,112]. 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 stan-dards for various age and gender 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 males and females need to be performed.

Physiologic 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 with this increase in HF is absent[176].

The autonomic nervous system response to athletic training and rehabilitative exercise programmes 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, with weightlessness and with the zero g that accompanies 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 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 HR range. β-adrenergic blockade was observed into 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, anaesthetics, 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-h and short 2 to 15-min 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[162,163,177] and a number of other pathophysiological conditions[177]. Using 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 heart rate variability is an important area of investigation, and it might provide early information about fetal and neonatal distress and identify those at risk for the 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 might also be possible through the proper application of these techniques.

Disease mechanisms

A fertile area of research is to use 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 the 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 neurologic disorders that accompany diabetes mellitus, alcoholism, and spinal cord injuries.

Conclusion

Heart rate variability has considerable potential to assess the role of autonomic nervous system fluctuations in normal healthy individuals and in patients with various cardiovascular and non-cardiovascular 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.

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Appendix A

Normal values of standard measures of heart rate variability

As no comprehensive investigations of all HRV indices in large normal populations have yet been performed,

Variable	Units	Normal values (mean ± SD)
Time domain analysis of nominal 24 h[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	n.u.	54 ± 4
HF	n.u.	29 ± 3
LF/HF ratio		1·5–2·0

some of the normal values listed in the following table were obtained from studies involving small number of subjects. The values should therefore have been 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.

The table lists only values of those measures of HRV which might be suggested for standardisation of further physiological and clinical studies.

Appendix B

Suggestion of procedures for testing of commercial equipment designed to measure heart rate variability

Concept
In order to achieve comparable accuracy of measurements reported by different commercial equipment, each device should be tested independently of the manufacturer (e.g. 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 (e.g. 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 other wise, 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, e.g. the test signal should be computer and/or hardware generated. Both brand new recorders as well as recorders which have been routinely used and routinely serviced for approximately a 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 analysing ECG records (such as Holter tapes) obtained with recorders of other manufacturers, each combination should be tested independently.

As 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 analyse 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 which should be introduced into such recordings should include different factors known to influence or potentially influence the precision of HRV assessment, e.g. variable noise levels, variable morphology of QRS signals which 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 (e.g. full 24-h test) rather than short-term tests should therefore 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 itemised in respect of features introduced into the recording, e.g. errors caused by increased noise, errors due to fiducial point wander, etc. 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

Members of the Task Force

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

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:

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