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Review

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Heart rate variability measurements and the prediction of ventricular arrhythmias

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Introduction

Heart rate variability (HRV) is the temporal variation between sequences of consecutive heartbeats. On a standard electrocardiogram (ECG), the maximum upwards deflection of a normal QRS complex is at the peak of the R wave (Figure 1), and the duration between two adjacent R wave peaks is termed the R-R interval. The ECG signal requires editing before HRV analysis can be performed, a process requiring the removal of all non-sinus-node-originating beats. The resulting period between adjacent QRS complexes resulting from sinus node depolarizations is termed the N-N (normal-normal) interval.[1] HRV is the measurement of the variability of the N-N intervals.

Although counter-intuitive, it is possible that HRV confers a survival advantage. Any system exhibiting intrinsic variability is primed to respond rapidly and appropriately to demands placed upon it.

HRV is a measure of the balance between sympathetic mediators of heart rate (HR) (i.e. the effect of epinephrine and norepinephrine, released from sympathetic nerve fibres, acting on the sino-atrial and atrio-ventricular nodes), which increase the rate of cardiac contraction and facilitate conduction at the atrio-ventricular node, and parasympathetic mediators of HR (i.e. the influence of acetylcholine, released by the parasympathetic nerve fibres, acting on the sino-atrial and atrio-ventricular nodes), leading to a decrease in the HR and a slowing of conduction at the atrio-ventricular node. Sympathetic mediators appear to exert their influence over longer time periods and are reflected in the low frequency power (LFP) of the HRV spectrum (between 0.04 Hz and 0.15 Hz.[2,3] Vagal mediators exert their influence more quickly on the heart, and principally affect the high frequency power (HFP) of the HRV spectrum (between 0.15 Hz and 0.4 Hz).[4] Thus, at any point in time, the LFP:HFP ratio is a proxy for the sympatho-vagal balance.

Physiological and pathological process may influence N-N interval variability. Under normal conditions, the balance between sympathetic and parasympathetic activity favours the latter. Physiological influences may modulate central and peripheral receptor (i.e. carotid sinus) activity. This is demonstrated in the slowing of HR with expiration, and a quickening with inspiration (respiratory sinus arrhythmia). These effects are apparent on the HFP spectrum. Circadian alterations in HRV are present in normal subjects, with higher LFP in the daytime and higher HFP at night.[5,6] Exercise, standing and stress in human subjects, and hypotension, and coronary or cerebral ischaemia in dogs, increases sympathetic drive and LFP. Conversely, cold stimulation of the face increases parasympathetic drive and increases HFP.[5–7]

In normal subjects, a variable heart rate is the normal physiological state. It has been suggested that the healthy heart has a long range 'memory' which prevents it from developing extremes of pace,

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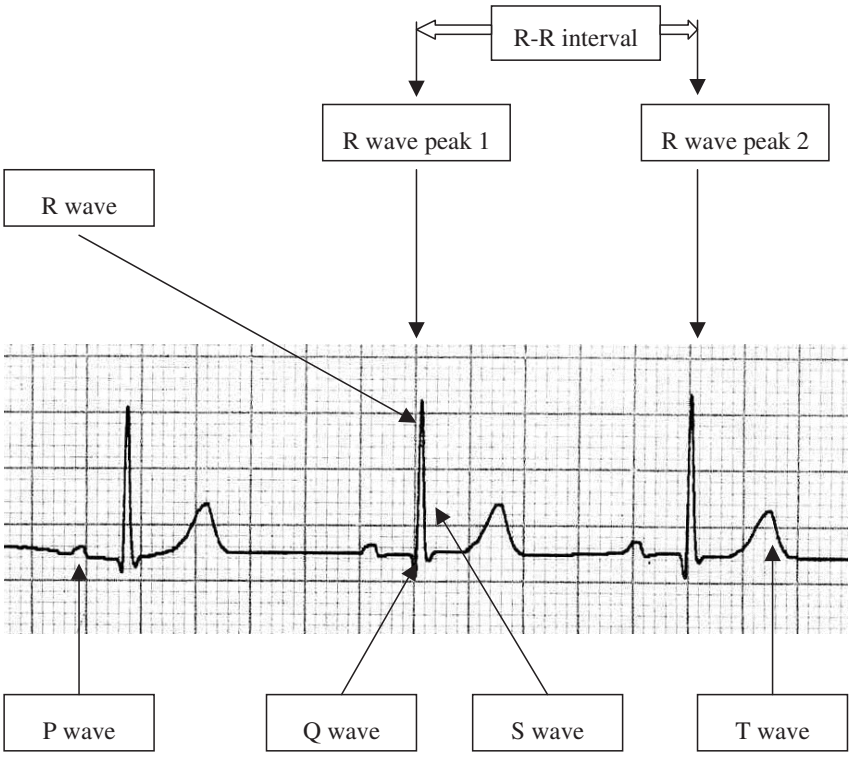

Figure 1. The normal electrocardiogram with component waves labelled.

and that this facility erodes as age or disease develops.[8] A loss of variability is associated with an increased mortality in patients post myocardial infarction.[9] In animal studies, an increase in sympathetic activity can provoke ventricular tachyarrythmias (VTAs)[10,11] and lower the ventricular fibrillation threshold.[12] This effect is exacerbated by coexistent myocardial ischaemia.[13,14] Conversely, vagal activity seems to provide a protective effect against the development of VTAs.[15,16] With this exerting the greatest effect on the heart rate in normal conditions and predominantly effecting HFP, a heart rate with much variability is the optimal state most likely to prevent the development of fatal VTAs.

Drug therapy may alter HRV; beta-blocker therapy has been shown to have a favourable effect on HRV[17,18] in patients with heart failure. However, changes in HR dynamics observed before VTAs in patients taking anti-arrhythmic drugs were independent of the drug regimen.[19]

The history of HRV

Heart rate variability (HRV) was first used clinically in 1965 when Hon and Lee[20] noted that fetal distress was accompanied by changes in beat-to-beat variation of the fetal heart, even before there was detectable change in the HR. In the 1970s, Ewing *et al.* used short-term HRV measurements as a marker of diabetic autonomic neuropathy.[21] In 1977, Wolf *et al.*[9] showed that patients with reduced HRV after a myocardial infarction had an increased mortality, and this was confirmed by studies showing that HRV is an accurate predictor of mortality post myocardial infarction (MI).[22–24] HRV falls within 2 to 3 days after MI, begins to recover within a few weeks, and is maximally but not fully recovered by 6 to 12 months.[25] Patients with persisting low HRV have mortality almost three times greater than those with a normal HRV.[23]

Over the last decade, alterations in HRV have been found in patients with many cardiovascular conditions. Patients with hypertension exhibit increased LFP and reduced circadian patterns,[26] congestive heart failure is associated with reduced vagal but preserved sympathetic activity,[27] and patients with denervated transplanted hearts show a 90% reduced HRV.[28] HR and ULFP may be good prognostic indicators for mortality, progression to surgery and the development of atrial fibrillation in patients with mitral regurgitation,[29] and patients with mitral valve prolapse show reduced HFP.[30] Radio frequency ablation of supraventricular arrhythmia pathways leads to an increase in HR, reduced HRV and vagal tone measurements,[31] and patients with cardiomyopathies exhibit reduced

vagal tone.[32] HRV has also been extensively investigated as a tool to predict the risk of sudden cardiac death. Low HRV is an independent risk factor for the development of later cardiac arrest in survivors of cardiac arrest.[33] Both reduced HF power and reduced LF power are independent predictors of later sudden death following survival from cardiac arrest. Reduction in HF power appears superior at risk-stratifying patients.[34] To date, most studies have concentrated on identifying HRV characteristics to predict the longer-term risk of developing fatal ventricular tachyarrhythmias (VTAs). Much less research has focussed on the changes that occur in HRV in the period immediately prior to the development of VTAs.

Problems with measuring HRV

To detect HRV changes over a period of hours or days requires a large volume of ECG data to be collected and analysed. This has traditionally been done with Holter devices that record the ECG in outpatients over periods from 24 h up to several weeks. Data can also be collected from patients who are monitored in hospital (Figure 2). Data capture on dynamic changes in HRV in the period prior to arrhythmias or ischaemic events is harder to attain, due to the relative infrequency of such events. In the laboratory environment, studies of patients with exercise or electrically-induced VT are possible, and implanted cardio-defibrillator devices (ICDs), are able to store information prior to an episode of ventricular fibrillation (VF) or ventricular tachycardia (VT).

Signal quality and elimination of background 'noise' is important when analysing HRV. Interpretation of HRV is extremely difficult in patients who are not in sinus rhythm (e.g. atrial fibrillation), or those with an extremely irregular HR (Figure 3) or multiple ectopic (VE) beats. Most HRV studies

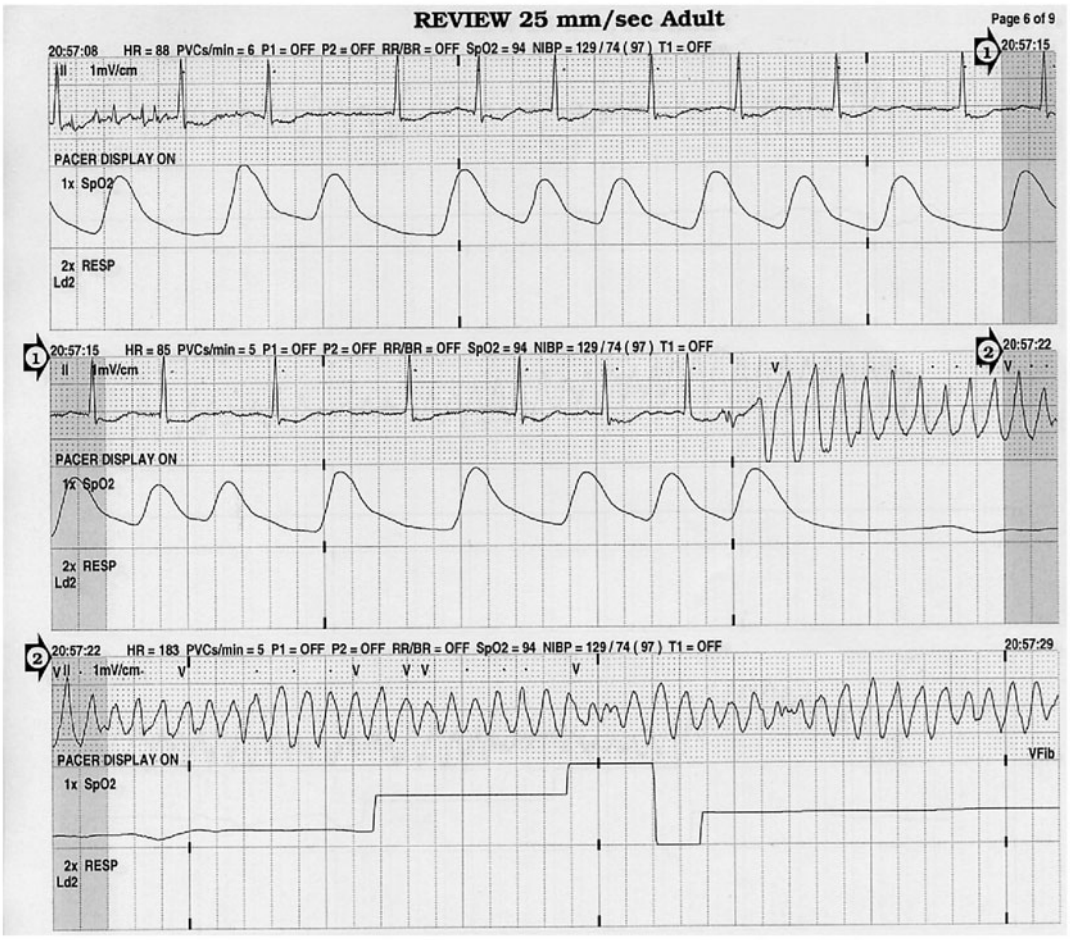

Figure 2. A section of an ECG waveform and oxygen saturation waveform obtained from an Emergency Department monitor. The ECG shows the onset of VF, with the accompanying loss of cardiac output demonstrated by the loss of the oxygen saturation waveform.

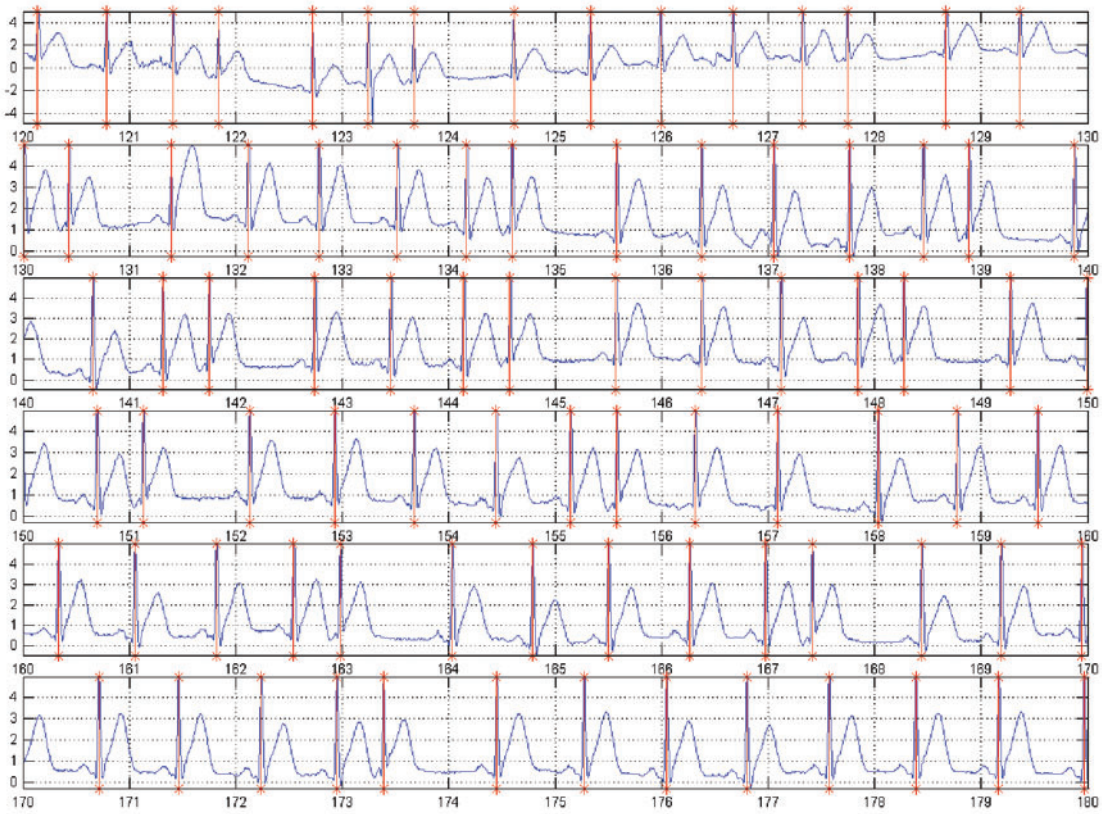

Figure 3. A section of an ECG signal obtained from a Coronary Care Unit, showing an irregular rhythm that makes HRV interpretation extremely difficult. The ECG demonstrates multiple premature atrial ectopic beats. The locations of the R wave peaks as detected by our R wave peak detection algorithm are represented by the vertical lines.

exclude patients who are not in sinus rhythm, but there is controversy over the issue of multiple VEs. Some authors advocate excluding signals that contain more than 10 ectopic beats per hour.[35] Others accept patients where ectopic beats comprise up to 5%,[19] 8%,[36] 10%[37,38] or even 15%[39] of all R-R intervals.

If a signal with ectopic beats is to be analysed, most authors advise removing the ectopic beats and correcting for them by adjusting the position of the R wave peak and placing a beat midway between the two adjacent beats. Editing algorithms are available that remove all R-R intervals that differ by a certain percentage from the preceding normal one. The level at which this editorial exclusion is performed (usually between 20–30% of the preceding R-R interval[40]) obviously reflects a balance between editing genuine data and missing ectopic beats. The frequency of ectopic beats is also of interest, since their frequency can increase prior to an arrhythmic event.[41] Since the vast majority of patients at risk of sudden cardiac death have underlying cardiac abnormalities and are more likely to have irregular rhythms such as atrial fibrillation and multiple VEs, the analysis of these signals is problematic. The process of signal editing prior to analysis is complex, and is poorly performed by conventional algorithms. Some authors suggest that manual filtering, although time consuming, is more accurate.

A final problem when measuring HRV is of accurately locating the successive R-wave peaks on the ECG. This requires a robust R-wave detector algorithm. The more accurate the R-wave detector, the less error in the analysed HRV spectrum. A completely missed R wave will cause greater error than a slightly miscorrected R wave, and this error is reflected more in the HFP than in the LFP of the HRV spectrum. This is due to the greater influence of a single N-N interval on short-term variability measures (HFP), compared to longer-term variability measures (LFP) where a single N-N interval effect becomes smoothed out.

Measuring HRV

HRV can be measured in time or frequency domains. Time domain methods are the simplest

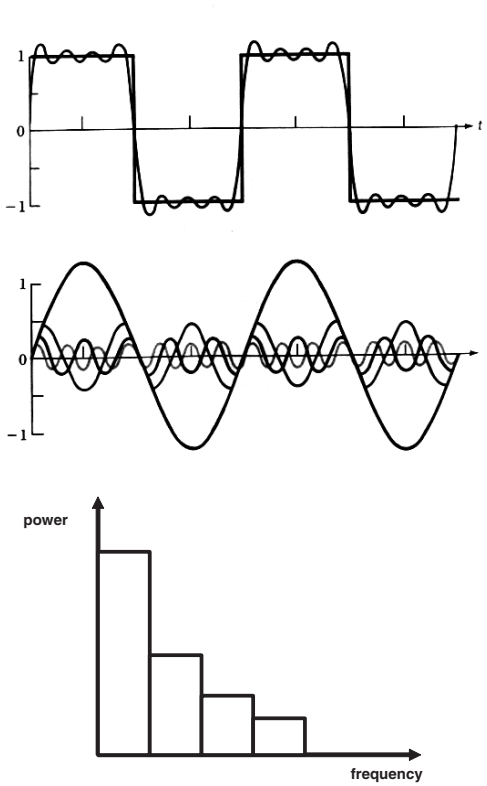

Figure 4. Any complex wave can be broken down into sine waves that when added together give the original complex wave. The figure shows the first four of the sine waves (middle) that when combined will make up the approximation to the square wave (top). The amplitudes of each sine wave are then converted to power and plotted against the frequency of the sine wave to give the power spectrum (bottom). To form the square wave, an infinite number of sine waves of decreasing amplitude are required. While this is a simplified example, it demonstrates the process of Fast Fourier Transform.

to perform. Each N (or R) point is determined in the ECG trace and variables such as mean HR and longest and shortest N-N intervals calculated. More complex calculations such as SDNN (standard deviation of the N-N intervals, representing the overall HRV) and NN50 (the number of adjacent N-N intervals that differ by more than 50 ms) can be performed using this data. Variables can also be derived that estimate the short- and long-term components of HRV (i.e. RMSDD, the square root of the mean squared differences between adjacent N-N intervals gives an estimate of short-term HRV, and SDANN, the standard deviation of the average N-N interval over periods of about 5 min, gives an estimate of long-term HRV). The calculation of all these variables enables the temporal variability of the HR to be quantified. The contribution of the various factors that manifest themselves in HF and LF HR changes can also be quantified (i.e. parasympathetic and sympathetic influences) and the interactions between them, preceding an event such as a VTA, quantified.

Spectral methods have been used to analyse HRV for 40 years.[42] These measure how the variance (or power) of the ECG signal changes as a function of frequency. Non-parametric methods of spectral analysis employing the Fast Fourier Transform (FFT) algorithm are commonly used.[1] This technique involves splitting the ECG waveform into small subunits (usually from 2 to 5 min long for the measurement of HFP, LFP and VLFP, but can be up to 24 h when analysing ULF components). These signal segments are then 'transformed' from a temporal signal into a spectral representation whereby the ECG signal is reinterpreted as the sum of multiple simpler (sinusoidal) waves of a given amplitude and frequency (Figure 4). The amplitudes of the component waves are then plotted to give a power spectrum by plotting power (the square of amplitude in volts) versus frequency.

VLFP, LFP and HFP components of the HRV can be calculated for recordings of 5 min or greater. For longer recordings of 24 h, ULFP can also be calculated, and reflects influences that occur on the heart rate over periods of days.

More recently, new time-frequency signal analysis methods have been used in the analysis of HRV. As their name suggests, these offer simultaneous interpretation of the signal in both time and frequency, which allows local, transient or intermittent components to be elucidated. (These are often obscured due to the averaging inherent within spectral-only methods, i.e. the FFT.) Several time-frequency methods are currently available, including the short time Fourier transform (STFT), Wigner-Ville transform (WVT), Choi-Williams distribution (CWD) and the continuous wavelet transform (CWT). Of these, the CWT has become the most favoured tool by researchers, as it does not contain the cross-terms inherent in the WVT and CWD methods, and provides frequency-dependent windowing, which allows for arbitrarily high resolution of the high frequency signal components (unlike the STFT)[43] (Figure 5). Accordingly, high frequency components (the 'fine detail' of the ECG signal) are not lost to analysis. CWT has recently shown an increase in LFP:HFP ratio prior to the onset of non-sustained VTA.[44] Other recent studies involving the wavelet analysis of HRV have allowed the detection of patterns directly associated with changes in myocardial perfusion,[45] and the association between autonomic tone and spontaneous coronary spasm in patients with variant angina.[46]

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