# Modern evaluation of the hypertensive patient: autonomic tone in cardiovascular disease and the assessment of heart rate variability

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Analysis of heart rate variability (HRV) permits an assessment of sympathetic and parasympathetic activity from EKG recordings. Analysis of HRV may be performed in both the time and frequency domain by the application of mathematical principles of signal processing. HRV demonstrates abnormalities in myocardial infarction, sudden death, heart failure, autonomic neuropathy and hypertension. The technique is useful for assessing prognosis and for evaluating therapeutic interventions. *Blood Press Monit* 4 (suppl 1):S7–S14 © 1999 Lippincott Williams & Wilkins.

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## Introduction

It has been widely recognized for centuries that variations in heart rate and blood pressure occur in a cyclical manner. Circadian, ultradian and infradian cycle variations have been observed in most biological systems; blood pressure and heart rate are no exception. Hales, in 1773, is credited with at least one of the first documented reports of beat-to-beat variation in arterial blood pressure [1]. Since 1965 variations in heart rate have attracted great interest since it has been determined to be an index of autonomic nervous system (ANS) function. Interest in heart rate variability (HRV) analysis has increased over the past two decades since it has been shown that a decrease in HRV is associated with increased cardiovascular mortality and that analysis of HRV provides insight into the function of the autonomic nervous system [2,3]. Cardiovascular conditions for which HRV measurements seem to be promising for determining prognosis and evaluation of therapeutic modalities are systemic arterial hypertension, ischemic heart disease and congestive heart failure (CHF).

The ANS has long been considered to play a role in the development of hypertension in some individuals [4–6]. This concept is based in large measure on the knowledge that the ANS is responsible for the short-term, i.e. minute-to-minute, control of blood pressure and heart rate. Thus, derangements in the ANS could easily be associated with sustained increases in blood pressure.

Abnormalities in the ANS are characteristic of patients with heart failure; abnormal activity of the parasympathetic nervous system (PNS) is one of the earliest abnormalities noted in the natural history of the syndrome [7,8,9]. Increased sympathetic nervous system (SNS) activity is associated with progressive deterioration and death either from progressive heart failure or sudden cardiac death, the latter often thought to be associated with cardiac arrhythmia.

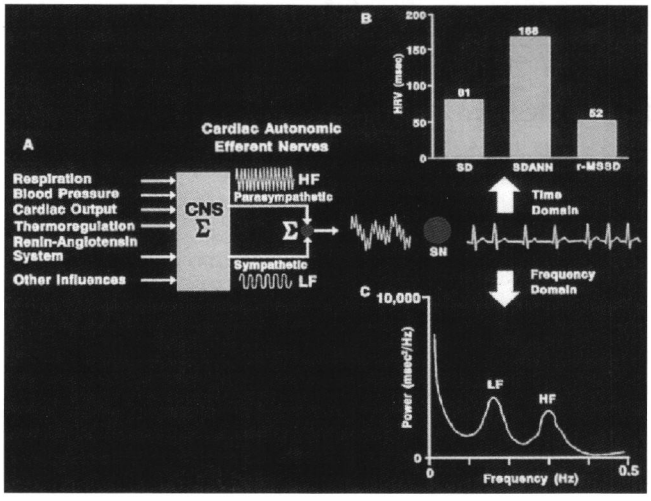
Based on the understanding of the important role of the ANS in the pathophysiology of hypertension and heart failure, it is little wonder that much interest has been generated in HRV analysis hoping that this technique would add important information concerning the pathophysiology of heart failure, prognosis and treatment modalities.

## Rationale for measuring HRV in hypertension and heart failure

Heart rate is determined by both the intrinsic firing of the pacemaker cells of the sino-atrial node and modulating influences of the ANS (Fig. 1). The ANS is composed of two divisions, the SNS, which innervates the sino-atrial node and which enhances firing rate, and the PNS, which exerts an inhibitory action, depressing spontaneous firing. Thus, the balance between the opposing ANS and PNS probably are the principal determinants of the heart rate.

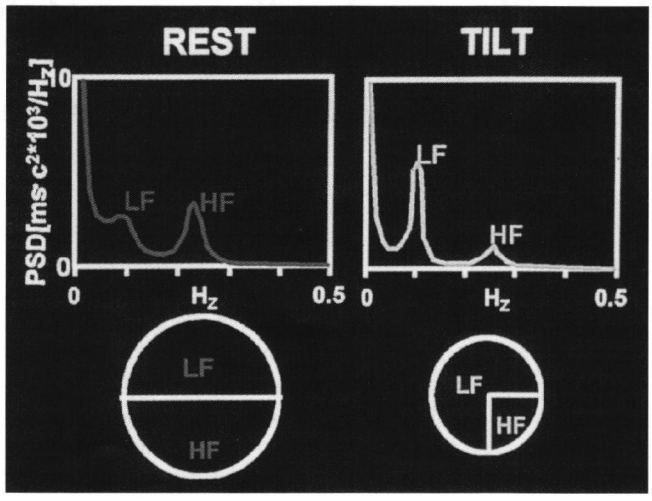
HRV represents the continual fine-tuning of the beat-to-beat control mechanisms. In the human, the heart rate is usually under a tonic vagal control. Vagal afferent stimulation leads to reflex excitation of vagal efferent activity and inhibition of sympathetic efferent activity, whereas the opposite effects are mediated by the stimulation of sympathetic afferent activity. Central vasomotor and respiratory centers and peripheral oscillation in arterial pressure and respiratory movements add additional control. Analysis of HRV may provide a means to infer the state and function of the central oscillatory, the SNS and PNS activity, humoral factors and the sinus nod. These inter-relationships are demonstrated by the effect on HRV by tilt (Fig. 2).

**Fig. 1**




Factors involved in producing variability in heart rate are illustrated. While the sympathetic (SNS) and parasympathetic (PNS) nervous sytems play a major role, other factors are also important. (Consult text for details.) CNS, central nervous system; HRV, heart rate variability; SDANN, standard deviation of all normal to normal beat intervals; r-MSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; HF, high frequency; LF, low frequency. Reproduced with permission [2].

**Fig. 2**




Effect of tilt on heart rate variability (HRV). Note that while total power decreases, the proportion of high frequency (HF) and low frequency (LF) components is altered. 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 LF and HF. During tilt, the LF component becomes dominant but, as total variance is reduced, the absolute power of LF appears unchanged compred with rest. Normalization procedure leads to predominant LF and smaller HF components, which express the alteration of spectral smaller HF components due to tilt. Pie charts show the relative distribution together with the absolute power of the two components represented by the area. During rest, the total variance of the spectrum was 1201 $ms^2$, and its VLF, LF and HF components were 586, 310 and 302 $m^2$, respectively. Expressed in normalized units (nu), the LF and HF were 48.95 and 47.78 nu, respectively. The LF/HF ratio was 1.02. During tilt, the total variance was 671 $ms^2$, and its VLF, LF and HF components were 265, 308 and 95 $m^2$, respectively. The LF and HF were 75.96 and 23.48 nu, respectively. The LF/HF ratio was 3:34. Thus, note that, for instance, the absolute power of the LF component was slightly decreased during tilt while the normalized units of LF were substantially increased.

Measurement of HRV is usually performed in either the time domain or in the frequency domain. Analysis of HRV in the time domain provides useful information regarding the integration of all of the variables, which influence beat-to-beat variation. These can be analyzed by both statistical and geometric means including the standard deviation of all normal–normal beat intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) and the 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) (HRV triangular index).

Analysis of HRV in the frequency domain permits the determination of the contributions of the SNS and PNS to overall beat-to-beat variation. The high frequency components of HRV (0.15–0.Hz) are primarily reflective of PNS activity, while medium frequency components (0.04–0.1Hz) are determined by activity of the SNS with minor contribution from the PNS.

There are some relationships between time and frequency domain measurements. The SDNN and HRV triangular index correlate with total power while the RMSSD correlates with high frequency.

It has been shown that an alteration in sympatho-vagal balance, i.e. a reduced parasympathetic tone or the predominance of sympathetic over parasympathetic activity, predisposes to cardiac arrhythmia. However, there is controversy regarding the concept that decreased HRV is simply a reflection of diminished parasympathetic input to the heart and therefore is a marker for the loss of vagal protection against proarrhythmic effects of premature depolarizations, excitation reflection and other arrhythmia-triggering mechanisms. Importantly, the time and technique of recording and analysis of HRV influence the data available for interpretation (see below).

In patients with hypertension, analysis of HRV in the frequency domain revealed evidence for an increase in SNS activity and a reduction in PNS activity [3]. Moreover, there was a blunting of circadian patterns. In a stratified random sample of 2061 subjects in the Atherosclerosis Risk in Communities (ARIC) cohort, analysis of HRV in both the time and frequency domains revealed significant trends of association of hypertension for low frequency/high frequency ratios and SDNN [10]. The results suggested that cardiac autonomic function is associated with prevalent hypertension, and that reduced vagal function and the imbalance of sympathovagal function are associated with the risk of developing hypertension. Similar findings have been reported from the Framingham Heart Study [11].

HRV has been studied in CHF to a greater degree than has hypertension [2,3]. Interestingly, the results are similar in that there is a reduction in spectral power at all frequencies with a disproportionate increase in low frequency (sympathetic) versus high frequency (parasympathetic) components of the power spectrum. Examination of Poincaré plots revealed that the more complex plots were associated with increased norepinephrine concentrations and greater sympathetic activation. Although the alterations of HRV are not closely correlated with the severity of the heart failure, the possible correlation with mortality may be better.

## Measurement of HRV

Although the concept of measuring HRV is well-founded on physiological principles, the methods for analysis continue to evolve. It is important for those who use data derived from analysis of HRV for research or clinical purposes to be aware of some of the inherent problems in recording and analysis.

### Data acquisition

Analysis of HRV is usually performed on a time series obtained from a 24 h ambulatory ECG recording. Analysis should ideally identify P–P intervals, but because this is technically difficult to do, R–R intervals are calculated; records with variable atrioventricular conduction abnormalities should not be analyzed as it is sino-atrial depolarizations that are of interest. The ECG signal is recorded on either analog tape or directly digitized on a 24 h ambulatory ECG recorder. Analog tape recording devices have an inherent problem with variable tape speeds that may introduce error into the recording system. Analog recorders should have internal clocks that provide correction for errors introduced by variable tape speeds. Digital recording devices perform the analog-to-digital conversion immediately, improving accuracy for identification of QRS peaks. Analog tape systems require an off-line computer to digitize the ECG signal for analysis.

The shortest possible time duration of an ECG recording for analysis is determined by the lowest frequency of interest, i.e. the lowest component frequency must be in the time domain record at least twice and preferably more. For example, if the lowest frequency of interest is 0.02 Hz and four cycles are desirable for analysis, then: 0.02 Hz/1 = four cycles/$X$, where $X$ = 800 s. Thus, 800 s of data need to be recorded in order to obtain four cycles of data at 0.02 Hz.

ECG recordings should be sampled at a sufficiently high rate to accurately locate the QRS peak in order to establish accurately R–R intervals [12,13]. A low-pass filter should have a cut-off frequency less than half the recording frequency, to prevent signal aliasing. Sampling rates of 128/s are industry standard and may be adequate for many patients. However, patients with very little HRV (e.g. severe heart failure, cardiac transplant) should be sampled at higher rates (probably at least 500 Hz) to prevent the introduction of 'jitter' into the recorded sample; 'jitter' produces spurious results when performing frequency domain analysis [12].

### QRS peak identification

Methods must be employed for removal of artifact and ectopic beats from the ECG recordings in order for the true QRS peaks to be located. All ectopic beats (using various algorithms) should be removed before generating a series of R–R intervals, particularly if frequency domain analysis is planned. Removal of non-sinus beats is generally performed using automatic computer algorithms followed by manual review. For research purposes, all records should be completely manually reviewed.

Some form of interpolation is employed to replace non-sinus beats. The abnormal beats are removed and an average R–R signal is substituted. This technique is called splining. Most investigators will exclude a segment of R–R values if 15% or more of the QRSs are abnormal.

The computer must 'recognize' the QRS peak before generating R–R intervals. Typically, the method involves taking the first derivative of the recording to localize the fiducial point. The maximum value is then found by searching within a few consecutive samples of the original signal [14,15].

### Generation of the interval function

After localization of each QRS peak, a computer file of R–R intervals is generated and a time series (interval function) calculated. Sampling of the interval function (interpolation) at regular intervals (usually 4 Hz) is performed [16]. Interpolation of data at a regular interval is necessary before using computer algorithms for frequency analysis. Several interpolation algorithms may be employed. Using a simple linear interpolation may introduce error into the frequency domain analysis and either a spline or cubic interpolation algorithm function may improve results.

### Power spectral density (PSD) calculation

Baseline trend removal is employed by removing the mean or by applying a linear trend removal algorithm once the interval function has been interpolated at a fixed sampling rate. This technique will remove the 'DC component' (zero frequency) of the signal. However, using a trend removal algorithm may affect the lower frequency components of the generated PSD function.

Methods for generation of the PSD include non-parametric [fast Fourier transform (FFT)] and parametric (autoregressive) methods. Both require that the time domain signal maintain stationarity. Either 5 or 10 min of data are usually analyzed to improve the likelihood that the time-generated signal is statistically stationary. Generation of a PSD is a second-order representation of a time series, therefore the time domain signal should exhibit second-order stationarity (i.e. mean and variance). The longer the time domain segment for analysis, the less likely it is to be stationary. To improve the likelihood of a stationary signal, patient recordings frequently are

made after a period of attaining a physiologic steady state. Investigators may visually inspect a time record for stationarity before PSD processing. Computer algorithms for evaluation of stationarity have been proposed and may improve HRV results [17–20]. Since a 24 h recording cannot be stationary, generation of 24 h PSD plots and subsequent measurements are of unknown value.

When applying the FFT the number of samples used for spectrum calculation (a value that is a power of 2 yields fastest computational results) should be identified. The variance of the PSD calculation can be reduced by breaking the entire signal into smaller overlapping sections, calculating an FFT and PSD for each section, and then averaging the PSDs (Welch segmenting) [21].

A windowing function applied to the time domain signal, prior to performing the FFT, improves the PSD. A non-rectangular window functions to decrease spectral leakage, while increasing the width of spectral peaks. Spectral leakage results from an assumption in the FFT algorithm that the time domain record is exactly repeated throughout the time period and also that signals within the time record are periodic at intervals corresponding to the length of the time record. The incomplete part of the sinusoidal wave in the time series does not correspond to its frequency on the PSD plot [22]. A window also reduces variance when using overlapping sections (Welch segmenting).

Each windowing function has its own characteristics and effects in the frequency domain. The main lobe is centered at each frequency component from the time domain signal and side lobes are generated. Windows are chosen based on the assumed properties of the original signal.

If the PSD has signals close to each other in frequency, then spectral resolution is important and a windowing function with a narrow main lobe (Hamming) would be chosen. If amplitude content of the PSD is more important than the exact location on the frequency axis, a window with a wide main lobe would be chosen [23].

The PSD may be normalized by dividing the variance of R–R fluctuations by the square of the mean heart rate. Power may also be normalized by using only the area under the PSD plot.

### Autoregressive (AR) methods for PSD estimation

AR methods for generation of the PSD generally have an advantage over the FFT in that a smoother spectrum can be generated and an accurate spectrum can be generated despite a relatively small sample size in the time domain. AR methods, also termed maximum entropy spectral estimation or linear-prediction spectral estimation, assume that the time domain signal is stationary, as do FFT techniques. The PSD based on the AR technique yields sharper frequency peaks compared to the FFT-based PSD.

The AR technique provides high resolution of the PSB, but may produce added spurious spectral peaks that are not actually present in the time series. An AR spectral model order may be chosen by representing what frequencies within the time series are expected. If it is assumed that a time signal has two sinusoidal waves as components, the model order number must be at least 4 (two peaks represent each sinusoidal—one is a positive frequency and the other a negative frequency). Otherwise the PSD resolution is too low. A model order that is too large yields results with extraneous detail [24].

## HRV in cardiovascular disease: prognosis and therapeutics

As detailed above, both time and frequency domain measures of HRV provide a measure of autonomic modulation of the heartbeat. Several pathophysiologic states have been linked to alterations in autonomic function. These include the development of new and recurrent myocardial infarction, presence of sustained and non-sustained ventricular arrhythmias, occurrence of cardiac arrest, and hemodynamic alterations resulting in syncope. Clinically alterations in HRV have been applied to the following clinical situations:

(1) Risk stratification following myocardial infarction.
(2) Prediction of early and late sudden cardiac death.
(3) Prognostication in patients with chronic CHF.
(4) Assessment of diabetic autonomic neuropathy.
(5) Risk prognostication in large general populations without overt clinical evidence of heart disease.
(6) Assessment of specific therapies.

### Post-myocardial infarction risk stratification

The utility of simple measures of HRV to predict total mortality in post-myocardial infarction patients using R–R variance computed over short time intervals was demonstrated by showing a 3.8% relative risk between high- and low-risk groups using a variance of 1000 $ms^2$ [25]. However, a low event rate prevented evaluation of the R–R interval analysis as an independent prognostic factor. Data from the Multicentre Post Infarction Research Group revealed HRV as an independent risk stratifier post-myocardial infarction [26]. In this retrospective analysis of 808 consecutive patients Holter recordings obtained 11 ± 3 days post-infarction demonstrated those with SDNN values less than 50 ms had a relative mortality 5.3 times higher than those with SDNN greater than 100 ms. This risk was independent of other well known risk factors including LV ejection fraction, age or PVC frequency. Other time domain measures including pNN50 were also predictive. The utility of frequency domain measures of HRV was demonstrated in 715 patients where 24 h ECG recordings found both time and frequency measures yielded similar prognostic information in prediction of total mortality [27]. However, in a multivariate Cox regression analysis ultra-low frequency power was the strongest predictor of all cause mortality while very low frequency power was the strongest predictor of arrhythmic death [28]. Another study using the HRV index confirmed the independent prognostic value of HRV [29]. These find-

ings have been confirmed by other groups [30,31]. HRV again proved useful in identifying high risk in 567 patients in the GISSI-2 study followed over a 3-year period [32].

The temporal evolution of HRV following acute myocardial infarction has been examined in two major studies: Using time domain techniques from 24 h recordings at selected intervals of up to 140 days post-infarction, anterior and inferior infarctions were shown to have differing HRV profiles [33]. Using frequency domain measures of HRV, it was shown that even at 12 months post-myocardial infarction recovery, values for the five selected measures were only one-third to one-half of age-matched controls [34]. These and other studies suggest that the final recovery values for HRV are the best predictors of subsequent events and for most patients these values have stabilized at 2–6 weeks post-myocardial infarction.

Even as early data confirmed the prognostic poser of HRV, it was also apparent that reliance on HRV analysis alone had limitations. Bayesian analysis demonstrated the positive predictive accuracy of HRV alone to be less than 50%, which prompted several studies to examine multivariate predictors. For example, a combination of R–R variability index below 20 ms, a positive signal-averaged ECG and presence of complex ventricular ectopy had a positive predictive accuracy of 58% [35]. The recently completed ATRAMI study [36] combined measures of HRV with baroreflex sensitivity and again demonstrated a greater than 50% predictive accuracy. Ongoing studies should clarify which combination of risk factors should be included to optimize predictive accuracy.

### Sudden cardiac death

A large body of experimental and clinical evidence suggests a link between lethal ventricular dysrhythmias and impaired autonomic regulation [37–39]. Survivors of ventricular fibrillation arrest exhibit very low HRV during morning hours when the incidence of sudden arrhythmic death is high [40]. A combination of HRV and inducible ventricular tachycardia has also been used to risk stratify patients at very high risk for sudden death [41]. A major potential utility of HRV concerns the ability of this technique to predict the short term occurrence of lethal ventricular tachyarrhythmias. A decreased HRV occurs in patients with spontaneous and inducible ventricular tachycardia compared to those with repetitive ventricular premature beats [42]. However, alterations in HRV were not found to precede ventricular tachycardia. Similarly, examination of 24 h Holter recording from patients who developed ventricular fibrillation found no short term alteration in HRV before the clinical event [43]. In contrast, another study found a decrease in HRV in all 17 patients studied who died during Holter recording [44]. As the total number of patients in these studies is small definitive statements on the use of HRV to predict short term clinical events can not be made.

### Prognostication in chronic CHF

Patients with left ventricular systolic dysfunction represent a complex syndrome with both preclinical and clinical presentations. In general patients with clinical CHF demonstrate marked neurohumoral activation, the extent of which correlated with a poor prognosis. In general patients with CHF regardless of etiology exhibit decreased HRV and absence of the usual diurnal variation in day–night HRV [45,46]. This reduction in HRV appears to be present even in patients with asymptomatic left ventricular dysfunction [47]. Most studies agree that given the high signal-to-noise ratio in patients with CHF, frequency domain analysis should be performed on long, rather than short, data sets.

A potential limitation of HRV analysis in CHF is the high prevalence of breathing abnormalities. In a consecutive study of 80 patients, 64% showed periodic or Cheyne–Stokes breathing patterns [48]. These abnormalities were associated with dominant power in the very low frequency band, potentially confounding the interpretation of the study.

## Prediction of risk in patients without clinical heart disease

The use of HRV analysis techniques to predicts clinical outcomes in general populations without overt heart disease has been examined in several large population studies. Data from the Framingham Heart Study [49] suggested that in an elderly cohort of patients a 1 SD in low frequency power was associated with a 1.70 times hazard for all-cause mortality. The Zutphen Study of 878 middle-aged Dutch men found low HRV to be predictive of mortality from all causes and suggested that low HRV to be predictive of mortality from all causes and suggested that low HRV was an indicator of compromised health in the general population [50]. In a study of 6693 patients who underwent Holter recording, 245 who died suddenly in a 2-year follow-up were found to have low short term HRV [51]. Low HRV was associated with a 4.1-fold higher risk for sudden death.

## Effect of specific therapies

Experimental studies have suggested that enhanced sympathetic activity and reduced parasympathetic activity facilitate the malignant potential of ventricular arrhythmias by altering ventricular fibrillation threshold. Thus interventions which restore autonomic 'balance' theoretically may provide protection from arrhythmic sudden death.

The effects of digoxin have been examined in several studies. In a randomized placebo controlled crossover study in normal subjects showed digoxin increased the vagal modulation of R–R intervals with an increase in high frequency power of 50% [52]. The effect of digoxin on 26 patients with CHF was examined [53]; a doubling of high frequency power was found indicating a large increase in cardiac vagal activity. Plasma norepinephrine also fell significantly. Thus digoxin enhances vagal activity in both normal patients and those with CHF. Perhaps this why this positive inotrope has a neutral effect on cardiovascular mortality in patients with CHF while other positive inotropes increase mortality.

The effects of beta blockade on HRV vary significantly depending on the population studied. As there is little sympathetic nervous activity in resting normal people the effects of beta blockers in normal patients at rest is small [54]. Propranolol blunted the marked increase in low frequency power that normally occurs with head up tilt [55]. When comparing the effects of atenolol to diltiazem on HRV, atenolol increased all parameters of vagal activity [56]. In patients with CAD, beta blockade flattened the circadian rhythm of the low frequency component by preventing its rise in the morning hours [57].

In patients with CHF several studies suggest an improved survival with low-dose beta blocker therapy. One mechanism of this effect may be restoration of sympathovagal imbalance. Carvedilol treatment in CHF patients resulted in a tripling of high frequency power, an increase of larger magnitude than seen in other studies [58].

Interventions which directly enhance vagal activity have been best studied with the use of transdermal scopolomine. In a study of normal patients, 24 h scopolomine patches caused a 2.5-fold increase of vagal activity as reflected by an increase in high frequency power [59]. Thirty-six patients, 4 days following an acute myocardial infarction, were treated with scopolomine [60] or placebo patches found substantial increases in both high frequency power and baroreflex sensitivity with scopolomine [53]. Whether this enhanced vagomimetic effect of low-dose scopolomine enhances prognosis remains to be established.

The effects of antiarrhythmic drugs has been less well studied. Flecainide decreases HRV in post-myocardial infarction patients but there is no correlation with mortality on follow-up [61]. Amiodarone does not alter time domain measures of HRV in patients with complex ectopy [62].

Studies demonstrating beneficial effects of angiotensin-converting enzyme (ACE) inhibitors has prompted several studies addressing their effects on HRV variability. Enalapril had no significant effect on R–R variability or autonomic response to head up tilt in a study of 20 normal subjects [52]. The effects of captopril on HRV were examined in 32 patients with class 3 heart failure using NN50 as a measure of parasympathetic activity; NN50 increased from a median of 482–1032 during treatment in patients with CHF and was unchanged in normal controls [63]. The authors speculated this effect was mediated by removal of cardiac vagal inhibition by angiotensin. An evolving consensus suggests augmentation of vagal tone may be an important mechanism in the protective effects of ACE inhibition.

## Conclusion

The analysis of HRV as a means of exploring the pathophysiology of disease, assessing prognosis and evaluating the effect of therapeutic interventions is still in a developmental phase. The concepts are deeply rooted in physiology and pathophysiology. While the analysis necessarily embraces mathematical concepts and techniques, the true value of HRV analysis in cardiovascular disease will only come from an integration of biological and medical disciplines with mathematical analysis.

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