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Current Clinical Applications of Heart Rate Variability

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Summary: Heart rate variability (HRV) has become a popular method for the studies of physiologic mechanisms responsible for the control of heart rate fluctuations, in which the autonomic nervous system appears to play a primary role. Depression of HRV has been observed in many clinical scenarios, including autonomic neuropathy, heart transplantation, congestive heart failure, myocardial infarction (MI), and other cardiac and noncardiac diseases. However, it is important to realize that clinical implication of HRV analysis has been clearly recognized in only two clinical conditions: (1) as a predictor of risk of arrhythmic events or sudden cardiac death after acute MI, and (2) as a clinical marker of evolving diabetic neuropathy. Recently, its role in evaluation and management of heart failure has also been recognized. It is pertinent to recognize the limitations of HRV as far as its clinical utility at present is concerned. The methodology of HRV had remained poorly standardized until the recent publication of the Special Report of the Task Force of ESC/NASPE, and thus has been presenting difficulty in comparing earlier existing data. Also, determination of the exact sensitivity, specificity, and predictive value of HRV, as well as the normal values of standard measures in the general population, still require further investigation before better standards can be set for existing and future clinical applications. This article reviews the major concepts of HRV measurements, their clinical relevance, and the recent advances in this field.

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Introduction

The fact that the beat of a healthy heart is not absolutely regular was noted by Albrecht von Haller in the eighteenth century,[1] but it is only within the last three decades that the clinical significance of heart rate variability (HRV) has been mentioned in the medical literature. In 1965, Hon and Lee[2] reported that the beat-to-beat interval changes are the first noted alteration before fetal distress occurs, even preceding any change in heart rate itself. Since then, the existence of physiologic rhythms within the oscillations of the interval between consecutive and instantaneous heart rates has been recognized, and at present the term "heart rate variability" has become generally accepted to describe the above variations.[3] Numerous studies have demonstrated that HRV measurements can prove useful in assessing the function of the autonomic nervous system with regard to cardiac function and can be reliable predictors in clinical medicine, as in the case of cardiac related morbidity and mortality.[4–7] This article reviews the major concepts of HRV measurements, their clinical relevance, and the recent advances in this field.

Measurement Techniques

In the evaluation of HRV, several methods can be applied which can be grouped into either the time domain or the frequency domain analysis.

Time domain analysis calculates a number of variables that describe either the heart rate at any time or determine the intervals between successive normal complexes. In a continuous electrocardiographic (ECG) recording, each QRS complex is detected and the normal-to-normal (N-N) intervals (intervals between consecutive QRS complexes originating from the sinus node) or the instantaneous heart rate are determined. Some simple calculated time domain variables include the mean N-N interval, the mean heart rate, the difference between the

shortest and the longest N-N interval, the difference between day and night heart rate, as well as the variations in instantaneous heart rate secondary to respirations, tilt, Valsalva maneuver, or phenylephrine infusion. From the above values, more complex statistical time domain measures can be calculated. They can be derived directly from measurements or from the differences of N-N intervals. The variety of time domain measures of HRV is summarized in Table I.

Considering the large number of different measures and the fact that many of these measures correlate closely with each other, the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (ESC/NASPE) has narrowed the number of necessary parameters for time domain HRV analysis to the following: (1) standard deviation of N-N intervals (SDNN) (estimate of overall HRV), (2) HRV triangular index (estimate of overall HRV), (3) standard deviation of averages of N-N intervals (SDANN) (estimate of long-term components of HRV), and (4) square root of the mean (RMSSD) (estimate of short-term components of HRV).[3]

Frequency domain analysis examines the periodic oscillations of a given heart rate at various frequencies. Power spectral density (PSD) analysis, one of the many spectral methods, provides the basic information of how power (variance) distributes as a function of frequency. Three main spectral components are distinguished in a spectrum calculated from short-term recordings (2–5 min): very low frequency (VLF), low frequency (LF), and high frequency (HF). Spectral analysis may also be used to analyze the sequence of beat-to-beat intervals of the entire 24-h period, providing the fourth spectral component, the ultra low frequency (ULF) (Table II).

To standardize physiologic and clinical studies, two types of recordings are recommended by ESC/NASPE: (1) short-term recordings of 5 min made under physiologically stable conditions processed by frequency domain methods, and/or (2) nominal 24-h recordings processed by time-domain methods. The data obtained with both methods appear to correlate well, but as the time domain analysis is technically simpler and less prone to interference, it is more applicable for clinical routine.[3]

Physiologic Correlates

Under normal conditions, heart rate and rhythm are the result of intrinsic cardiac automaticity and the modulating influence on the autonomic nervous system. Vasomotor and respiratory centers (central oscillators) and arterial blood pressure fluctuations with respiratory-related hemodynamic changes (peripheral oscillators) provide further modulating factors. This modulation results in short- and long-term heart beat-to-beat interval and rate periodic fluctuations.[8] The analysis of HRV permits deductions on the state and function of the central oscillators, autonomic efferent activity (both the sympathetic and the vagal components), humoral factors, and the sinus node. It provides us with a useful tool for detecting and assessing individual components of the autonomic control of the heart.

Spectral analysis of HRV has been especially useful in providing information on sympathovagal balance and its modulatory effect on the heart period. The efferent vagal activity appears to be a major contributor to the HF component, as evidenced by changes in the HF spectrum component in response to autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy.[8–10] Interpretation of the LF component is more controversial.

TABLE I Selected time domain measures of heart rate variability[3]

Variable	Units	Description
Statistical measures		
SDNN	Ms	Standard deviation of all N-N intervals
SDANN	Ms	Standard deviation of the averages of N-N 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 N-N intervals
SDNN index	Ms	Mean of the standard deviations of all N-N intervals for all 5 min segments of the entire recording
SDSD	Ms	Standard deviation of differences between adjacent N-N intervals
NN50 count		Number of pairs of adjacent N-N intervals differing by >50 ms in the entire recording; three variants are possible, counting all such N-N interval pairs in which the first or the second interval is longer
pNN50	%	N-N50 count divided by the total number of all N-N intervals
Geometric measures		
HRV triangular index		Total number of all N-N intervals divided by the height of the histograms of all N-N intervals measured on a discrete scale with bins of 7.8125 ms (1/128 s)
TINN	Ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all N-N intervals
Differential index	Ms	Difference between the widths of the histogram of differences between adjacent N-N intervals measured at selected heights
Logarithmic index		Coefficient φ of the negative exponential curve $ke^{-\varphi t}$, which is the best approximation of the histogram of absolute differences between adjacent N-N intervals

Abbreviation: HRV = heart rate variability.

TABLE II Selected frequency domain measures of heart rate variability[3]

Variable	Units	Description	Frequency range
Analysis of short-term recordings (5 min)			
5 Min total power	Ms^2	The variance of N-N intervals over the temporal segment	≈<0.4 Hz
VLF	Ms^2	Power in VLF range	<0.04 Hz
LF	Ms^2	Power in LF range	0.04–0.15 Hz
LF norm	NU	LF power in normalized units LF/(total power − VLF) × 100	
HF	Ms^2	Power in HF range	
HF norm	NU	HF power in normalized units HF/(total power − VLF) × 100	
LF/HF		Ratio LF [ms^2] / HF [ms^2]	
Analysis of entire 24 h			
Total power	Ms^2	Variance of all NN intervals	≈<0.4 Hz
ULF	Ms^2	Power in ULF range	<0.003 Hz
VLF	Ms^2	Power in VLF range	0.003–0.04 Hz
LF	Ms^2	Power in LF range	0.04–0.15 Hz
HF	Ms^2	Power in HF range	0.15–0.4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	≈<0.04 Hz

Abbreviations: VLF = very low frequency, LF = low frequency, HF = high frequency, ULF = ultra low frequency, NU = normalized units.

Some authors consider LF as a marker of sympathetic modulation, while others consider it to be a parameter that includes both sympathetic and vagal influences.[8, 9, 11–13] In long-term recordings, the HF and LF components account for only approximately 5% of total power. Although the ULF and VLF components account for the remaining 95% of total power, their physiologic correlates are still unknown.[3]

In normal subjects, spectral analysis of 24-h recordings reveals that 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.[8, 14] Low and high frequency can increase under different conditions. An increase in LF 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. Conversely, an increase in HF is induced by controlled respiration, cold stimulation of the face, and rotational stimuli.[3]

Clinical Relevance

The apparently easy derivation of HRV has provided cardiologists with a seemingly simple noninvasive tool for both research and clinical studies. However, the significance and meaning of the many different measures of HRV are much more complex than generally appreciated, as is pointed out in the Special Report of the Task Force of ESC/NASPE.[3] Accordingly, even though the number of studies that employ HRV has increased dramatically and novel HRV measures have recently been introduced, it is important to recognize that the clinical relevance of HRV has been clearly demonstrated in only two clinical conditions: (1) Impaired HRV can be used alone or in a combination with other factors to predict risk of arrhythmic events after myocardial infarction (MI), and (2) decrease in HRV is a useful clinical marker for evolving dia-betic neuropathy.[3, 15] Recently, utility of HRV analysis has been increasingly recognized in predicting an increased risk of cardiac death in patients with left ventricular dysfunction.

Heart Rate Variability as Risk Stratifier after Acute Myocardial Infarction

In survivors of MI, HRV decreases early after acute infarction and starts to recover within a few weeks.[16] The mechanism for this transient reduction in HRV is not yet clearly defined, but the derangements in neural activity of cardiac origin seem to be involved. It is suggested that the changes in the geometry of a beating heart due to necrotic and noncontracting segments may abnormally increase the firing of sympathetic afferent fibers by mechanical distortion of the sensory endings.[16, 17] This sympathetic excitation attenuates the activity of vagal fibers directed to the sinus node. Accordingly, in patients after an acute MI, a predominance of the sympathetic activity and a reduction in parasympathetic tone have been demonstrated.[4, 7, 18] It is the sympathetic activation that predisposes to ventricular fibrillation, while increased vagal tone appears to be protective against malignant ventricular tachyarrhythmias. Thus, patients after acute MI are more prone to ventricular arrhythmias. It is of interest to note that not only are beta blockers reported to attenuate the proarrhythmic increase of sympa-

thetic activity after acute MI, but there also appears to be an enhancement of the parasympathetic tone evidenced by the increase in HRV. It is speculated that both mechanisms contribute to the protective role of beta blockers in those patients. These effects of beta blockers are also thought to be responsible for their protective role in patients with heart failure.[19–22]

The degree of respiratory sinus arrhythmia shows a linear relation with parasympathetic control and its assessment may be considered as a prognostic tool in patients who have suffered from MI.[8,16] The investigators in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial (GISSI-2) have shown HRV to be affected in a similar manner in patients treated with fibrinolysis during an acute MI.[23] This observation is pertinent since most of the earlier studies were conducted before the introduction of fibrinolysis.

St. George's group in London has demonstrated that HRV is as powerful as ejection fraction for predicting total cardiac mortality after MI, whereas it is superior for predicting sudden death and sustained ventricular tachycardia.[23] Even though the independence of the predictive value of HRV from other traditional risk markers has been shown, the positive predictive value of HRV analysis used as a single factor is low, and thus combined analysis of HRV and other well-known risk parameters should be used.[24,25] The combination of impaired HRV and late potentials, for instance, has been shown to have a much higher sensitivity, a better positive predictive value, and a higher relative risk for arrhythmic events, and was superior to those incorporating left ventricular function, exercise ECG, and frequency of ventricular premature beats.[16,24] However, it remains to be determined which other stratification parameters are the most practical and most feasible to be combined with HRV for multifactorial risk stratification.[3,16] Currently, it is recommended by the ESC/NASPE Task Force that HRV should be determined 7 to 10 days post infarct from 24-h Holter recordings for the purpose of predicting mortality and arrhythmic complications in postinfarction survivors.

Currently, data are also available to support the predictive power of HRV for arrhythmic events and death in unselected patient populations, documenting a 4.1-fold higher risk for sudden cardiac death in patients with depressed than with preserved HRV.

Other Clinical Situations

The denervated hearts of patients after cardiac transplantation provide a unique model for understanding cardiac autonomic innervation. As a result of the lack of innervation, there is a greatly reduced total spectral power and there are no distinct spectral peaks of HRV in the hearts of these patients. After an interval of more than a year, predominantly low-frequency spectral components might appear that are thought to reflect possible cardiac reinnervation. The most important observation for clinical practice seems to be the potential of HRV to detect rejection episodes in the transplanted heart. In this setting, the total power was found to be increased because of overall chaotic irregularities without the presence of periodic components; however, the value of these observations as an early sign of allograft rejection still requires confirmation.[26,27]

Congestive heart failure has been found to be associated with the activation of the sympathetic nervous system, and correspondingly depressed HRV, including suppressed diurnal heart rate variations.[28] As mentioned earlier, as is the case in patients post acute MI, beta blockers appear to exert a significant protective effect also in patients with heart failure by attenuating the increased sympathetic tone and restoring the diminished parasympathetic tone. Several studies have shown a significant relationship between depressed HRV and New York Heart Association functional class, which implies that HRV can be used for the purpose of follow-up.[29] It is also of interest that successful treatment of cardiac failure in general, for example, with angiotensin-converting enzyme inhibitors, may result in restoration of HRV.[26,30]

Attempts have been made to establish the role of HRV analysis in patients with cardioneurogenic syncope. Autonomic withdrawal has been shown in these patients, either in both sympathetic and parasympathetic components without changing the sympathovagal balance, or in purely parasympathetic components.[31]

The assessment of HRV may also be a useful tool for predicting the progression in aortic valvular disease and the necessity for surgery. Patients with either aortic stenosis or regurgitation, who required cardiac surgery, have been found to have decreased time and frequency domain indices.[32,33]

Impaired HRV is a widely accepted marker of diabetic autonomic neuropathy, which appears to support the assumption that impaired cardiac autonomic innervation is part of a more widespread autonomic neuropathy affecting small nerve fibers in all organs. A reduction in the time-domain parameters of HRV, which are easy to analyze, appears to detect neuropathy before its clinical expression. Power spectral analysis of HRV demonstrates a reduction in absolute power of both LF and HF components and is an even more accurate test. At present, HRV analysis has become a fully established clinical test for risk stratification and subsequent management of diabetic patients.[26,34]

The significance of decreased HRV in patients with major depressive disorder is still not fully understood. These patients have a higher risk of cardiovascular mortality, which correlates with the decrease in HRV. There appears to be an association of increased HRV with successful treatment of this disorder, which may reflect improved autonomic function, and thus it is speculated that this could decrease the risk of cardiovascular mortality.[35,36]

Other postulated applications of HRV analysis include its usefulness in the monitoring of patients with significant brain damage, where a correlation between decreased HRV and severe brain damage has been made.[37,38]

Conclusion

Heart rate variability has become a popular method for the studies of physiologic mechanisms responsible for the control

of heart rate fluctuations, in which the autonomic nervous system appears to play a primary role. Depression of HRV has been observed in many clinical scenarios, including autonomic neuropathy, heart transplantation, congestive heart failure, MI, and other cardiac and noncardiac diseases. However, it is important to realize that clinical implication of HRV analysis has been clearly recognized in only two clinical conditions: (1) as a predictor of risk of arrhythmic events or sudden cardiac death after acute MI, and (2) as a clinical marker of evolving diabetic neuropathy. Recently, its role in the evaluation and management of heart failure has also been recognized.

It is pertinent to realize the limitations of HRV as far as its clinical utility at present is concerned. The methodology of HRV had remained poorly standardized until the recent publication of the Special Report of the Task Force of ESC/NASPE, resulting in the difficulty of comparison of the earlier existing data. Also, determination of the exact sensitivity, specificity, and predictive value of HRV, as well as the normal values of standard measures in the general population, still requires further investigation before better standards can be set for existing and future clinical applications. The measurement of HRV appears to be a well established research tool and is useful in the assessment of the function of central and peripheral modulators involved in the control of the heart's beat-to-beat variability. Its clinical applicability still remains limited because of the complex methodology and lack of standardization.

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