Heart Rate Variability for Risk Stratification of Life-Threatening Arrhythmias

[The following is a position statement prepared by the Cardiovascular Technology Assessment Committee: LEONARD S. DREIFUS, MD, FACC, Chairman, JAI B. AGARWAL, MBBS, FACC, ELIAS H. BOTVINICK, MD, FACC, KEITH C. FERDINAND, MD, FACC, CHARLES FISCH, MD, FACC, ex officio, JOHN D. FISHER, MD, FACC, J. WARD KENNEDY, MD, FACC, ex officio, RICHARD E. KERBER, MD, FACC, CHARLES R. LAMBERT, MD, FACC, OKIKE N. OKIKE, MD, FACC, ERIC N. PRYSTOWSKY, MD, FACC, SANJEEV V. SAKSENA, MBBS, FACC, JOHN S. SCHROEDER, MD, FACC, ex officio, DAVID O. WILLIAMS, MD, FACC. This position statement was approved by the Board of Trustees of the American College of Cardiology on March 13, 1993. Reprints are available from: Educational Products Sales and Marketing; 9111 Old Georgetown Road; Bethesda, MD 20814; 800/257-4740.]

Description

The variation and fluctuation of the heart rate in relation to the mean heart rate have been shown to be a function of cardiorespiratory physiology. It has been known for several decades that enhanced vagal tone has a salutary effect on the electrophysiologic properties of the ventricle to prevent the emergence of life-threatening ventricular arrhythmias in certain situations, particularly in postinfarction and diabetic patients. Hence, heart rate variability may offer information about sympathetic and parasympathetic autonomic function and could serve as a measure of risk stratification for serious cardiac arrhythmias and possible sudden cardiac death. Notably, continuous changes in the sympathetic-parasympathetic balance can be reflected in variations of the sinus rhythm that oscillate around the mean heart rate. Hence, small adjustments in heart rate are engendered by cardiovascular control mechanisms. These mechanisms may involve respiratory movement, gas exchange, chemoreflex, intrathoracic pressure changes, thermoregulation and peripheral vascular resistance alterations that can affect the respiratory centers and, consequently, cardiovascular centers.
Animal Models

In animal models, enhanced vagal tone has produced an increase in the ventricular fibrillation threshold. Increased vagal tone antagonizes the effects of enhanced sympathetic tone, shortening ventricular refractoriness and heightening, in at least one model, baroreceptor response that may prevent initiation of ventricular fibrillation. These effects may indicate a link between a low baroreceptor sensitivity index, as demonstrated with phenylephrine injections in humans after myocardial infarction, and a group of patients at increased risk of dying. Furthermore, in patients with long-standing diabetes and parasympathetic dysfunction, a corresponding marked reduction in sinus arrhythmia or other indexes of vagal tone seems to be associated with an increased risk of sudden death. Thus, measures of vagal tone may have prognostic clinical significance.

Measurement of Heart Rate Variability

Heart rate variability has been used to study sympathovagal balance (1,2). Several methods have been proposed to measure heart rate variability. Two very simple methods used for many years are 1) the measurement of sinus rate variability with breathing at a fixed rate of 5 or 6 breaths/min, and 2) the Valsalva index, which measures the ratio between the shortest RR intervals during phase II and the maximal RR interval during phase IV. More recently, analysis of the 24-h Holter ambulatory electrocardiogram (ECG) has been used to measure heart rate variability (3). Methods to analyze heart rate variability employ both time and frequency domain measurements that quantify periodicities in the data. Prognostic information to risk stratify patients for future ventricular arrhythmias or other cardiac events leading to premature death may be possible by quantifying heart rate variability. Recently, a detailed review of the physiology of heart rate variability by van Ravenswaaij-Arts et al. (4) summarizes the clinical use of this technology.

Diagnostic Accuracy

Depending on the method used to evaluate heart rate variability, several inaccuracies can be introduced. It is very important that artifacts or premature complexes in the recording not be included in the analysis or there can be possible miscounting of heart rate due to sensing of the T wave. Miscounting of heart rate can add inaccuracy to the system.

Cost

Several Holter systems already employ heart rate variability in the analysis algorithm (3). The cost of this procedure does not appear to be excessive at the present time. As with other new
diagnostic methods, there could be a hidden cost of heart rate variability testing if clinical decisions are based on its results and lead to further diagnostic tests or therapy.

Safety

The technique appears to be safe. It is noninvasive and free of electrical hazards.

Comparison With Alternative Technologies for Risk Stratification

Postmyocardial infarction patients. Depending on the condition being studied, several alternative methods are available for risk stratification. In patients after myocardial infarction, assessment of left ventricular function, measurements of baroreceptor sensitivity, quantification of ventricular arrhythmias during 24-h Holter ambulatory ECG recording, signal-averaged ECG studies and electrophysiologic testing have all been used to determine risk for subsequent sudden death. Exercise testing and other measures to evaluate ischemia are also important in this patient group. Kleiger et al. (5) recently reported a weak correlation between time and frequency domain measures of heart rate variability and more traditional risk predictors. When Farrell et al. (3) analyzed risk stratification for arrhythmic events in postmyocardial infarction patients utilizing heart rate variability, ambulatory ECG variables, signal-averaged ECG and left ventricular function; they found that impaired heart rate variability was most predictive of future arrhythmic events. However, when impaired heart rate variability was combined with the presence of late potentials on the signal-averaged ECG, the sensitivity was only 58%. Baroreflex sensitivity assessed with phenylephrine injection weakly correlated with heart rate variability.

Patients with congestive heart failure. These patients are also clearly at increased risk for sudden death. Risk stratification has included many of the same tests used for postmyocardial infarction patients, and heart rate variability has also been shown to be decreased in this condition. In one investigation by Kienzle et al. (6), measures of heart rate variability were not significantly related to left ventricular ejection fraction, although some were weakly correlated with cardiac output. There were suggestions from this study that a stronger correlation occurred with measurements of sympathoexcitation. Few data are available regarding risk stratification using heart rate variability in these patients.

Unanswered Questions

Two major questions concerning heart rate variability remain to be clarified. First, many methods to measure heart rate variability have been reported, and it is very difficult to conclude which one is most appropriate for establishing normal values and for particular patient subgroups. In a recent study, Bigger et al. (7) evaluated 12 separate measurements of time and frequency domain
analysis. There is a need to standardize the measurement of heart rate variability and to quantify normal values under various circumstances, including patient age and gender. Second, the sensitivity, specificity and predictive accuracy of this test require much more prospective investigation. Correlations of this test with other risk stratification measurements will be necessary to evaluate its independent predictive value. The preliminary data available do not allow for definitive conclusions.

Furthermore, the value of heart rate variability or any other risk stratification test in patients who undergo revascularization of infarcting myocardium requires assessment. It appears that mortality after myocardial infarction is decreasing with the new and aggressive therapeutic methods being used, and heart rate variability will have to be evaluated in this setting. Similar evaluations need to be performed in other pathophysiologic states such as congestive heart failure.

Future Research

Prospective multicenter studies should be undertaken to determine the sensitivity, specificity and predictive accuracy of heart rate variability in various situations, particularly in patients after acute myocardial infarction (8-12) and in those with congestive heart failure (2,6,13,14). It will be necessary to assess whether heart rate variability testing alone or in combination with other variables is an important predictor of sudden cardiac death (8,15-17) both in survivors of cardiac arrest (8,15,16) and in patients with chronic heart disease who appear to be at risk for cardiac arrest. Recent studies by Dougherty and Burr (15) in survivors of sudden cardiac arrest demonstrated that 1-year mortality in the survivor group was inversely related to several variables, including age, standard deviation of all RR intervals and low frequency spectral power. Determination of normal values and of optimal time and frequency domain measurements to be used should be made with the use of appropriate control groups. It is important to evaluate patients with similar ages and disease states because these variables can affect heart rate variability. Normal values in a relatively small series were reported by Huikuri et al. (17) (Table 1). Further studies should be stratified for age and gender and should utilize both fast Fourier analysis and autoregressive methods.

Status

Heart rate variability is a very interesting method of evaluating parasympathetic and sympathetic effects on heart rate in humans, and preliminary data suggest it could become an important prognostic tool. There are substantial unanswered questions that preclude heart rate variability from being a standard clinical test at present; until more data are known it should be considered as a clinical investigation.
References


**Table 1. Twenty-Four-Hour Average Heart Rate Variability**

<table>
<thead>
<tr>
<th></th>
<th>Survivors of Cardiac Arrest (n = 2')</th>
<th>Control Patients (n = 22)</th>
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<tbody>
<tr>
<td>SD of RR intervals (ms)</td>
<td>29 ± 10</td>
<td>51± 15*</td>
</tr>
<tr>
<td>High frequency spectral area (ms² x 10)</td>
<td>13 ± 7</td>
<td>28 ± 14†</td>
</tr>
<tr>
<td>Low frequency spectral area (ms² X 10)</td>
<td>14 ± 13</td>
<td>22 ± 12</td>
</tr>
<tr>
<td>Ratio between low and high frequency areas</td>
<td>1.2 ± 0.9</td>
<td>0.9 ± 0.3</td>
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*p < 0.001, †p < 0.01, comparing survivors of cardiac arrest and control patients. Data are adapted, with permission, from Huikuri et al. (17).