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Measurement of Heart Rate Variability: A Clinical Tool or a Research Toy?

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OBJECTIVES The objectives of this review are to discuss the diversity of mechanisms that may explain the association between heart rate (HR) variability and mortality, to appraise the clinical applicability of traditional and new measures of HR variability and to propose future directions in this field of research.

There is a large body of data demonstrating that abnormal HR variability measured over a 24-h period provides information on the risk of subsequent death in subjects with and without structural heart disease. However, the mechanisms responsible for this association are not completely established. Therefore, no specific therapy is currently available to improve the prognosis for patients with abnormal HR variability. Reduced HR variability has been most commonly associated with a risk of arrhythmic death, but recent data suggest that abnormal variability also predicts vascular causes of death, progression of coronary atherosclerosis and death due to heart failure. A consensus is also lacking on the best HR variability measure for clinical purposes. Time and frequency domain measures of HR variability have been most commonly used, but recent studies show that new analysis methods based on nonlinear dynamics may be more powerful in terms of risk stratification.

Before the measurement of HR variability can be applied to clinical practice and used to direct therapy, more precise insight into the pathophysiological link between HR variability and mortality are needed. Further studies should also address the issue of which of the HR variability indexes, including the new nonlinear measures, is best for clinical purposes in various patient populations. (J Am Coll Cardiol 1999;34:1878–83) © 1999 by the American College of Cardiology

Analysis of heart rate (HR) variability from electrocardiographic (ECG) recordings has become an important method for assessing cardiovascular autonomic regulation. Despite a large body of literature concerning HR variability in cardiology and medical journals during the last decade (>2,000 publications, Fig. 1), its measurement from the Holter recordings has not yet become a routine clinical tool. Since the observations by Kleiger et al. (1) that low standard deviation in N-N intervals (SDNN) analyzed from a 24-h ECG implied an increased risk of dying within three to four years after an acute myocardial infarction (AMI), studies in a number of different populations have confirmed these relationships (2–15). Recently, a prospective multicenter survey confirmed the previous results of retrospective studies (16). Recent data also show that analyses of HR variability by new methods based on nonlinear dynamics may perform even better than the traditional measures in risk stratification (17–19). Despite intensive research on various aspects of HR variability, it is not yet fully established why patients with abnormal HR variability die earlier than those with normal variability. An understanding of mechanisms linking abnormal HR variability to increased mortality might lead to specific therapeutic strategies that may reduce the risk of death for high risk patients.

The aims of this article are to provide a critical review of our current knowledge of the potential reasons why abnormal HR variability may increase mortality, to appraise the clinical applicability of traditional and new methods of measuring HR variability and to propose future directions for HR variability research.

WHY DOES LOW HEART RATE VARIABILITY PREDICT MORTALITY?

Most analyses of the HR variability data support the observations that it is a predictor of sudden arrhythmic death (19–24), based largely on epidemiological follow-up studies. More recent work has shown that low HR variability is also a predictor of nonarrhythmic cardiac events, such as myocardial infarction (12), rapid progression of atherosclerosis (25) and death from heart failure (15).

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Abbreviations and Acronyms

AMI = acute myocardial infarction
ECG = electrocardiogram
HR = heart rate
SDNN = standard deviation of N-N intervals

HR variability and arrhythmic death. A number of observational studies have shown that low HR variability is an independent predictor of sudden cardiac death (3–6,9,10,13). In fact, it has been suggested that HR variability may be a better marker for increased risk of arrhythmic events than any other noninvasive measure (3,9,10,26). Despite the general acceptance that low HR variability is a marker of increased risk of arrhythmic death, there are many problems associated with the interpretation of the results that are used to support this concept. The lack of a definition of the exact mode of death is a major problem in epidemiological follow-up studies. Sudden death has been commonly attributed to arrhythmia, but recent data based on stored ECGs of patients with implantable cardioverter-defibrillators indicate that more than half of the deaths defined as sudden (e.g., occurring within 1 h of the onset of symptoms) are not arrhythmic (27,28). Even if stricter criteria are used for defining arrhythmic death (29), all definitions lack specificity with respect to defining the exact mode of death. The definitions of arrhythmic events used in epidemiological studies also tend to vary; some equate the category of arrhythmic events with resuscitated ventricular fibrillation; others use sustained ventricular tachycardia, resuscitated ventricular fibrillation and sudden death as a combined end point (10,26).

The incidence of both nonsudden and sudden death among patients surviving an AMI has declined significantly during the past two decades (1,30–32). As all deaths occurring suddenly are not arrhythmic, the true incidence of arrhythmic deaths is probably less than 2% per year in consecutive survivors of AMI discharged from the hospital with the best available therapy (32). In view of the low number of deaths and the uncertainties about the mode of death in epidemiological follow-up studies, even a large multicenter survey (16) may not be able to give a definite answer regarding the value of HR variability as a predictor of arrhythmic death.

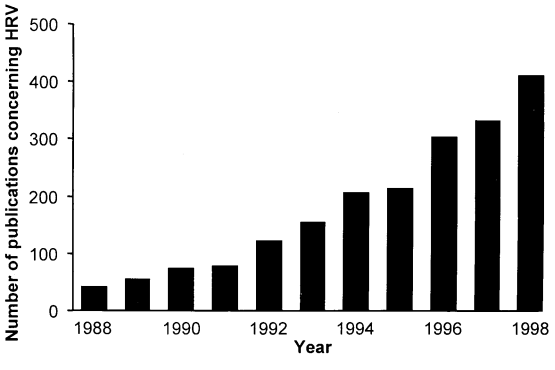

Figure 1. The annual number of publications dealing with HRV during the last decade based on search from the MEDLINE system using the key word "heart rate variability." HRV = heart rate variability.

In case-control studies, HR variability has been compared between survivors of documented arrhythmic events and matched controls without a history of life-threatening arrhythmia (33,34). These studies do not have the problem of uncertainty about the mechanisms of arrhythmic events, but there may be some problems in careful matching of the patients with respect to all possible variables that could influence their vulnerability to arrhythmic events and the measures of HR variability. In general, case-control studies have shown that HR variability is lower in arrhythmia patients than in controls (33,34), but significant overlapping in the measures of HR variability has been observed between the two groups.

Analysis of HR behavior before the onset of life-threatening arrhythmias could potentially provide insight into the role of abnormal HR variability in the onset and perpetuation of ventricular tachyarrhythmias. Data from ambulatory recordings suggest that HR variability is altered before the spontaneous onset of ventricular tachyarrhythmic events, suggesting that abnormal variability may predispose the patient to the onset of arrhythmias (35–38) or at least mark the presence of a transient trigger. These observations are based on relatively small numbers of selected patients, however, and are, to some extent, controversial (35–38).

Studies in animals have convincingly shown that abnormal autonomic regulation predisposes them to life-threatening arrhythmias (39). Such experiments have used acute coronary occlusion as a model for defining the role of the autonomic nervous system in the genesis of arrhythmias (39,40). The responses of this system to acute coronary occlusion have been shown to predict ischemia-induced ventricular fibrillation. Also, the baseline reflex autonomic function, expressed as baroreflex sensitivity, has been shown to predict ventricular fibrillation during subsequent coronary occlusion in dogs without prior myocardial necrosis, whereas baseline tonic autonomic function, expressed as HR variability, does not (39). Acute coronary occlusion during balloon angioplasty results in variable and unpredictable changes in HR variability in humans (41,42). Recent data have shown that the response of HR variability to acute coronary occlusion is predictive of ischemia-induced complex ventricular ectopic activity, but the baseline HR variability is not (43). Together, these observations support the view that the responses of the autonomic nervous system to acute hemodynamic changes or ischemia may be more important in the genesis of life-threatening arrhythmias than the baseline autonomic regulation, expressed as HR variability.

These epidemiological, case-control and experimental

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data do not provide definite proof that the patients with abnormal HR variability have an increased risk of experiencing a life-threatening arrhythmia event. To achieve that goal, randomized intervention studies in the patients with abnormal HR variability are needed to confirm the widely accepted concept of an association between low HR variability and vulnerability to arrhythmic death. One pilot study, the Nordic ICD study, involved the implantation of a cardioverter-defibrillator in 33 patients with low HR variability and impaired left ventricular function after an AMI. During the median follow-up of 22 months, only one patient experienced an appropriate shock from the device (44). This suggests that low HR variability, measured as SDNN, in combination with a reduced ejection fraction measured in the convalescent phase of AMI, has a low accuracy for predicting the occurrence of life-threatening arrhythmic events.

HR variability and coronary events. Epidemiological studies have provided evidence that abnormal HR variability also predicts mortality in the general population. Data from the Framingham Study show that low SDNN is a predictor of death in the elderly (7), and data in younger subgroups among the same cohort showed that low HR variability predicts the occurrence of various adverse cardiac events (12). In another unselected elderly population, abnormal long-term HR variability predicted an increased risk of dying during the 10-year follow-up (14). All these studies including random samples of subjects from the general population have shown that abnormal HR variability predicts various vascular events such as angina pectoris, myocardial infarction and stroke mortality (7,12,14). These data support the view that abnormal HR variability is not only a marker of arrhythmic death, but also predicts a number of other cardiac and vascular events.

It has been shown recently that reduced HR variability and elevated 24-h HR predict the progression of human coronary atherosclerosis as assessed in serial quantitative coronary angiograms (25). Fast HR has been observed to predispose to the rapid progression of atherosclerosis in several animal models (45–47). The explanation of the associations observed between HR, HR variability and the progression of atherosclerosis may lie in the hemodynamic factors. Progression of coronary lesions has been shown to result from the effects of HR on blood flow dynamics at the arterial wall (45,48). The effects of elevated HR and low HR variability on the progression of coronary atherosclerosis may well explain the finding that reduced SDNN predicts late mortality better than early mortality in AMI patients treated with modern thrombolytic therapy (8). Sudden arrhythmic death is known to occur most commonly in the early phase after the acute cardiovascular event (49), and the progression of atherosclerosis and the occurrence of new coronary events are more likely mechanisms of later death. It should be noted in particular that rapid progression of coronary artery disease is also common in other patient populations with low HR variability and fast HR, e.g., diabetics and cardiac transplant recipients.

HR variability and progression of heart failure. Heart failure is a common mechanism of death among patients surviving a large AMI. Despite the improved therapeutic options, progressive heart failure still remains an important contributor to cardiovascular mortality. Although HR variability has been shown to be impaired in the patients with heart failure (50), earlier studies have not pursued the notion that low HR variability may be a prognostic marker of death from progressive heart failure. Since reduced HR variability and elevated HR reflect the degree of neurohumoral activation caused by impaired cardiac pump function, they may influence left ventricular remodeling and the progression of heart failure. A recent large study has shown that low SDNN predicts death due to progressive heart failure but not the sudden death of patients with congestive heart failure (15).

Considered together, the data suggest that abnormal HR variability is a general risk marker for all common modes of cardiac death: arrhythmic, vascular and hemodynamic. Neurohumoral activation and altered sympathovagal interaction are the most common mechanisms of abnormal HR variability of patients with heart disease. It is not surprising that abnormal HR variability is able to predict various causes of death, as neurohumoral and sympathetic activation contribute to arrhythmogenesis, progression of heart failure and atherogenesis (51,52).

METHODS OF MEASURING HEART RATE VARIABILITY

There are numerous indexes that describe quantitative and qualitative aspects of the oscillations of the R-R interval around its mean value (53). An ideal method for clinical work would be a single HR variability index that could be calculated reliably on the basis of a simple, widely available analytical method. At the moment, there is no consensus about the best available index of HR variability for clinical use, despite the efforts of the Task Force of the North American Society of Pacing and Electrophysiology and the European Society of Cardiology to unify and standardize the methodology (53). Noisy data, artifacts, trends and ectopic beats are the major practical problems encountered in HR variability measurements. Reviews of these problems are described in detail elsewhere, and only some points are discussed here (54,55).

Traditional methods for analyzing HR variability. Twenty-four hour ambulatory recordings are most commonly used to assess the prognostic significance of HR variability (1–12). Recordings made under uncontrolled conditions over a 24-h period are always subject to noise, unstationarities, artifacts and premature beats with variable coupling intervals and compensatory pauses. Despite improvements in computer techniques for processing R-R interval data, meticulous manual editing is needed to iden-

tify and label the R-R intervals as "normal beats" or "abnormal beats," a technique that is prone to subjective bias. Various automatic algorithms have been developed to exclude artifacts and ectopic beats from the sinus intervals. R-R intervals that differ by more than 20% to 30% from the preceding ones are usually automatically excluded in time-domain analysis and the gaps filled by various methods in the spectral analysis of HR variability. All these methods are arbitrary. It is obvious that the 20% to 30% rule will exclude some genuine data, particularly in high-risk patients who often show abrupt changes in sinus intervals (56). On the other hand, ectopic beats with a long coupling interval may remain unedited. The most reliable analysis of HR variability can be obtained from subjects without ectopic beats, but this is often not the case in the patients with heart disease. Varying figures are used for the minimum number of qualified sinus beats required for the data to be acceptable for analysis, ranging from 99% to 70%. The most strict criteria do not allow recordings with >10 premature beats/h (57), but some investigators have included only patients with >10 premature beats/h (6,37). It should be noted, however, that 20% to 30% of all high-risk patients in post-AMI populations are usually excluded from any analysis of HR variability due to frequent ectopy, artifacts or episodes of atrial arrhythmias. None of the follow-up studies has reported a mortality rate for these patients, but it may well be even higher than for patients with low HR variability.

The most commonly used prognostic HR variability index has been the SDNN analyzed over a 24-h period (1,2,7,8). The geometric triangular analysis methods developed by Malik et al. (58) perform as well as the traditional time-domain analysis methods for risk stratification and do not suffer from the bias of human editing, but they are not widely available in commercial analysis systems. Spectral analysis of HR variability allows assessment of frequency-specific fluctuations in HR behavior and provides prognostic information beyond the time-domain measures (6). The spectral methods are invalidated for wide clinical applications by their numerous technical problems, e.g., the even more prominent influence of ectopy and unstationarity on the results than in statistical or geometrical methods. Poincarè plot analysis of R-R intervals allows visual and quantitative analysis of instantaneous and continuous R-R interval variability and also provides more powerful prognostic information on patients with heart failure and on arrhythmic risk than the traditional time-domain methods (11,36). Although all the statistical, geometrical and spectral measures of HR variability differ in their manner of computation and analysis, these methods are fundamentally based on moment statistics and describe the magnitude of HR variability. It is therefore not surprising that the traditional nonspectral measures, including quantitative Poincarè plot analysis and the spectral measures all have a relatively close mutual correlation (59), and that there are only minor differences in prognostic power between them. The average 24-h HR also correlates relatively well with all the traditional measures of HR variability (61), and one study has shown that the prognostic information provided by the average 24-h HR is almost as powerful as that obtained from a measurement of time domain HR variability (9).

New methods of analyzing HR variability based on nonlinear dynamics. Analytic methods derived from nonlinear dynamics based on chaos theory and fractal mathematics have opened new approaches for studying and understanding the characteristics of HR behavior (60,61). These methods differ from the traditional measures of HR variability in that they are not designed to assess the magnitude of variability. Rather, they estimate the correlation properties and complexity of HR variability and other features in HR dynamics that are not uncovered by methods based on means and variance. It is notable that only a weak correlation exists between these new nonlinear measures and traditional measures (62,63). Methods of analyzing the fractal-like correlation properties of HR behavior have been most commonly used to detect abnormalities in R-R interval dynamics in various cardiovascular disorders (13,14,18,62,63).

Several studies suggest that nonlinear dynamics may be involved in the genesis of HR variability (60–63), but the clinical applicability of the methods based on nonlinear dynamics has not been tested in large-scale studies until recently (13,14,17–19). Analysis of 1/f characteristics, i.e., the inverse power-law slope, has provided prognostic information beyond the traditional HR variability measures in two populations (13,14). Data on the patients with depressed left ventricular function show that fractal analysis of HR variability yields more powerful prognostic information than the traditional nonspectral and spectral measures (18,19) (Fig. 2). Altered fractal properties of R-R intervals have also been shown recently to precede the spontaneous onset of ventricular fibrillation without evident abnormalities in traditional indexes of HR variability (63). Of particular note is the fact that some fractal analysis techniques do not require preprocessing or editing of premature beats which may be of practical importance. Fractal analysis methods seem at present to be promising means in risk stratification, but more prospective studies in other populations performed by independent investigators will be needed to establish their clinical utility.

FUTURE DIRECTIONS

There are a number of commercial analytical systems that can reliably detect and measure R-R intervals from ambulatory recordings and calculate various indexes of HR variability. Manufacturers use a variety of methods for dealing with ectopic beats and artifacts and for analyzing nonspectral and spectral HR variability indexes. The development of these software systems has not been guided in any way but has been left to free market forces (64).

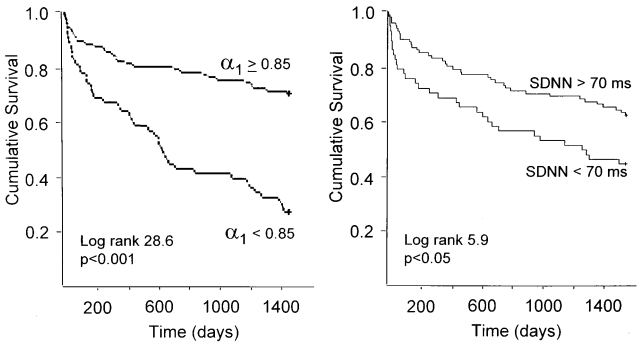

Figure 2. Kaplan-Meier survival curves for the patients with the short-term fractal-like scaling exponent ($\alpha 1$) <0.85 or ≥ 0.85 and for the patients with the standard deviation of all N-N intervals (SDNN) <70 ms or >70 ms included in the placebo arm of the TRACE study. Short-term scaling exponent was a better predictor of mortality than standard deviation of all N-N intervals in these postinfarction patients. Modified from "Fractal Analysis of Heart Rate Dynamics as a Predictor of Mortality in Patients With Depressed Left Ventricular Function After Acute Myocardial Infarction." (18) with permission. SDNN = standard deviation of N-N intervals.

Similarly, no standardization has been established for the various commercial systems. More research will still be needed to compare the prognostic value and clinical utility of the various traditional and new HR variability measures before an ideal index can be introduced for clinical intervention purposes and for development by commercial manufacturers.

Before the measurement of HR variability can be considered to be of any clinical value, however, therapeutic interventions are needed in the patients who present with abnormal values. Ongoing research (65,66) should provide important information on whether antiarrhythmic therapy can improve the survival of patients with impaired left ventricular function and low 24-h HR variability. Trials aimed at preventing the progression of heart failure in such patients by means of modern pharmacological agents should also be of clinical importance, as will trials estimating the effects of antiatherogenic therapy on progression of atherosclerosis of patients with fast HR and low HR variability. Pharmacological or nonpharmacological interventions should be sought for improving 24-h HR variability. It will also be important to study whether an improvement in HR variability can actually prevent mortality in order to avoid the misconception of the 1980s that abolishing premature ventricular beats with antiarrhythmic drugs could reduce mortality.

Before the results of the abovementioned ongoing and planned research efforts are available, the measurement of HR variability by various methods remains a fascinating research toy but not a routine clinical tool. If the intensive research into various aspects of HR variability continues to increase exponentially as it has done during the last decade, it is possible that the measurement of a simple HR variability index will become a routine clinical procedure comparable with the measurement of blood pressure or plasma cholesterol in the not-too-distant future.

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