Measurement of Heart Rate Variability by Methods Based on Nonlinear Dynamics

Heikki V. Huikuri, MD, Timo H. Mäkikallio, MD, and Juha Perkiömäki, MD

Abstract: Heart rate (HR) variability has been conventionally analyzed with time and frequency domain methods, which measure the overall magnitude of R-R interval fluctuations around its mean value or the magnitude of fluctuations in some predetermined frequencies. Analysis of HR dynamics by methods based on chaos theory and nonlinear system theory has gained recent interest. This interest is based on observations suggesting that the mechanisms involved in cardiovascular regulation likely interact with each other in a nonlinear way. Furthermore, recent observational studies suggest that some indexes describing nonlinear HR dynamics, such as fractal scaling exponents, may provide more powerful prognostic information than the traditional HR variability indexes. In particular, short-term fractal scaling exponent measured by detrended fluctuation analysis method has been shown to predict fatal cardiovascular events in various populations. Approximate entropy, a nonlinear index of HR dynamics, which describes the complexity of R-R interval behavior, has provided information on the vulnerability to atrial fibrillation. There are many other nonlinear indexes, eg, Lyapunov exponent and correlation dimensions, which also give information on the characteristics of HR dynamics, but their clinical utility is not well established. Although concepts of chaos theory, fractal mathematics, and complexity measures of HR behavior in relation to cardiovascular physiology or various cardiovascular events are still far away from clinical medicine, they are a fruitful area for future research to expand our knowledge concerning the behavior of cardiovascular oscillations in normal healthy conditions as well as in disease states. **Key words:** Holter recording, chaos, myocardial infarction.

Heart rate variability is usually analyzed with time and frequency domain methods, which measure the overall magnitude of R-R interval fluctuations around its mean value, or the magnitude of fluctuations in some predetermined frequencies (1). These measures have been used to detect alterations of autonomic cardiovascular regulation in many physiological conditions and disease states (1). Analysis of HR dynamics by methods based on chaos theory and nonlinear system theory has gained recent interest. This interest is based on observations suggesting that the mechanisms involved in cardiovascular regulation likely interact with each other in a nonlinear way. Therefore, methods based on the nonlinear system theory have been constantly developed (2–8).

From the Division of Cardiology, Department of Internal Medicine, University of Oulu, Oulu.

Reprint requests: Heikki Huikuri, Division of Cardiology, Department of Internal Medicine, University of Oulu, Kajaanintie 50, 90220 Oulu, Finland; e-mail: heikki.huikuri@oulu.fi

0022-0736/03/360S-0021$30.00/0
doi:10.1016/j.jelectrocard.2003.09.021

The fundamental problem in selecting a valid mathematical model for analysis of heart rate dynamics is that we deal with the system in which we cannot record all the effecting variables and the total number of degrees of freedom is not exactly known. Therefore, for diagnostic and clinical purposes, the applicability of different methods should be tested in specific populations. In this article we have focused to review the methods most widely used and tested in various clinical settings.

Methods of Nonlinear R-R Interval Dynamics

Numerous algorithms have been developed to describe dynamic fluctuation of heart rate data and a variety of different nonlinear methods have been used for analysis of R-R interval dynamics in different clinical situations. Geometrical analyses, several types of different fractal scaling measures, power-law analyses, different complexity measures, and various symbolic measures have been tested and used in various patient populations (9–15).

Power-law Heart Rate Variability Analysis

A plot of spectral power and frequency on bilogarithmic scale and the slope of this relation provide an index for long-term scaling characteristics of heart rate data (4). The slope is typically calculated for very low frequencies. This slope has been found to be altered among patients with cardiovascular disorders (9). In normal patients, the power-law slope is equal to -1 and becomes steeper, eg, after myocardial infarction (9).

Detrended Fluctuation Analysis

Detrended fluctuation analysis (DFA) quantifies the presence or absence of fractal correlation properties of R-R intervals and has been validated for time series data. It was developed to characterize fluctuations on scales of multiple lengths. The self-similarity occurring over a large range of time scales can be defined for a selected time scale with this method. The details of this method have been described by Peng et al. (2). This measure is partly related to changes in the spectral characteristics of heart rate behavior. The ratio of the low- to high-frequency spectral components correlates with the short-term scaling exponent of detrended fluctuation analysis, particularly when breathing is controlled, but when recordings are done in “free running” situations like 24-hour Holter recordings the association is weak. Therefore, fractal correlation properties may be more suitable to probe subtle alterations in heart rate dynamics than simple spectral ratios.

Complexity Measures

Lyaponov exponent is a quantitative nonlinear measure to evaluate how chaotic the system is (16). The feasibility of this method is limited in heart rate variability analysis, because it requires large data sets and system to remain stable over the recording time, which biologic systems seldom do. By the Haussdorff correlation dimension D, complexity of system can be measured, but it has limited value in heart rate variability analysis due to large error of estimation. Therefore, it is more convenient to evaluate the correlation dimension D_2 from a heart rate time series (17). The pointwise correlation dimension (18) is a measure that overcomes the limitation of large data sets by allowing operations with short and instationary data. Another quantity of the characterization of deterministic chaotic activity is Kolmogorov entropy K, which refers to system randomness and predictability (19). It can also be estimated only from large data sets limiting its practical applications.

Approximate entropy measures the regularity and complexity of time series data by quantifying the likelihood that runs of patterns that are close remain close on next incremental comparisons (20,21). The larger the value of approximate entropy, the greater the unpredictability in the R-R interval time series. The input variables m and r must be fixed to compute approximate entropy. The variable m determines the length of compared runs of R-R interval data, and the variable r sets the tolerance for the comparison of these runs. Although approximate entropy can be calculated from relatively short data sets, the amount of data points has an influence on the approximate entropy.

Return Maps

Two-dimensional Poincaré plots method (also called return maps) is a geometrical method, which provides a beat-to-beat visual and quantitative analysis of R-R intervals (22,23). This quantitative method of analysis is based on the notion of different temporal effects of changes in the vagal and sympathetic modulation of heart rate on the subsequent R-R intervals without a requirement for a stationary quality of the data. The shape of the plot can be used to classify the signal into one of several classes (22,23), and the irregular shapes quantified from Poincaré plots may then be classified as nonlinear. In quantitative analysis, short-term RR interval variability and long-term RR interval variability of the plot can be separately quantified (23).

Methodological Considerations

Whether various nonlinear methods detect nonlinear behavior of signal dynamics is an important scientific issue, but from the practical point of view it is more important to know whether they are applicable for clinical purposes. Concepts of nonlinear dynamics, fractals, inverse power-law, entropy and other terms used in the context with newer analysis methods of heart rate variability refer more to mathematics than to medicine, and may be received by some skepticism by clinicians. However, there is increasing evidence from multiple studies to support the clinical utility of the analysis methods based on nonlinear dynamics. The main results of the clinical studies using nonlinear analysis techniques are summarized below.

Clinical Studies Using Methods Based on Nonlinear Heart Rate Dynamics

The ability of spectral power-law slope to predict death after myocardial infarction was first reported by Bigger et al. (9). In their study, a steep power law slope was a powerful predictor of all-cause mortality or arrhythmic death and predicted these outcomes better than the traditional power spectral bands. In addition to patients with myocardial infarction, long-term scaling properties have been observed to predict mortality among randomly selected general elderly population (11).

Recently, analysis of short-term fractal properties of heart rate fluctuation by the DFA method has provided superior prognostic power compared to conventional measures among patients with acute myocardial infarction and depressed left ventricular function (10,12). First, short-term fractal-like correlation properties of R-R intervals were studied in 159 patients with acute myocardial infarction and left ventricular ejection fraction $<35\%$ with 4-year follow-up (13). Among analyzed variables, reduced scaling exponent showed to be the best predictor of mortality (13). More recently, in a larger population of 446 survivors of acute myocardial infarction with a left ventricular ejection fraction $<35\%$, reduced short-term fractal exponent was the most powerful heart rate variability measure as a predictor of all-cause mortality (10). Reduced fractal exponent predicted both arrhythmic death and nonarrhythmic cardiac death. Recently the prognostic power of short-term fractal scaling index has also been demonstrated among more general population of patients with myocardial infarction and broad variation in their left ventricular systolic function (24).

Patients with chronic heart failure have also shown altered fractal organization in heartbeat dynamics (2), and moreover, altered fractal correlation properties have been observed to be related to mortality among patients with chronic congestive heart failure (25). More recently, the predictive power altered short-term scaling exponent has also been observed in large-scale heart failure population with 24-hour electrocardiographic recording (26). In addition to patient populations with advanced cardiovascular disease, short-term scaling exponent has shown to be powerful predictor of cardiac mortality among more general patient population (27).

In addition to life-threatening arrhythmias, altered nonlinear dynamics have been observed also before the spontaneous onset of atrial fibrillation among the patients without a structural heart disease (28). When heart rate variability indices were analyzed in 20-minute intervals before 92 episodes of spontaneous, paroxysmal atrial fibrillation in 22 patients without structural heart disease, traditional measures showed no significant changes before the onset of atrial fibrillation. However, a progressive decrease occurred both in approximate entropy and short-term fractal exponent before the onset of atrial fibrillation episodes, showing that changes in the complexity and fractal properties precede the spontaneous onset of atrial fibrillation in patients with no structural heart disease. These values were also lower before the onset of atrial fibrillation compared with values obtained from matched healthy control patients. Reduced entropy values indicating larger predictability in heart rate dynamics have been reported also to precede spontaneous episodes of atrial fibrillation after coronary artery bypass surgery (29).

Conclusions and Future Perspectives

Research of heart rate variability has increased exponentially during the last decade. Methods derived from nonlinear system theory have shown new insights into the abnormalities in heart rate behavior in various pathological conditions, providing additional prognostic information as compared to traditional heart rate variability measures, and clearly complement the conventional analysis methods. Despite statistical data suggesting predictive power of various heart rate variability indexes, none of these methods are in widespread clinical use at the moment, because no trial has adequately linked the reliability of any of these variables to clinical outcome with an intervention. Therefore, more clinical studies by using new and traditional methods of heart rate variability will be needed, before the clinical applicability of these methods can be definitively established.

References

1. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heat rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 93:1043, 1996
2. Peng CK, Havlin S, Stanley HE, et al: Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 5:82, 1995
3. Pincus SM, Goldberger AL: Physiologic time-series analysis: what does regularity quantify? Am J Physiol 226:H1643, 1994
4. Saul JP, Albrecht P, Berger RD, et al: Analysis of long-term heart rate variability: methods, 1/f scaling and implications, in Computers in Cardiology. Silver Spring, MD, IEEE Computer Society Press, 1987, p 419
5. Skinner JE, Pratt CM, Vybiral T: A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. Am Heart J 125:731, 1993
6. Yamamoto Y, Hughson RL: Coarse-graining spectral analysis: New method for studying heart rate variability. J Appl Physiol 71:1143, 1991
7. Goldberger AL: Nonlinear dynamics, fractals and chaos: Applications to cardiac electrophysiology. Ann Biomed Eng 18:195, 1990
8. Goldberger AL: Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. Lancet 347:1312, 1996
9. Bigger JT Jr, Steinman RC, Rolnitzky LM, et al: Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. Circulation 93:2142, 1996
10. Huikuri HV, Mäkikallio TH, Peng CK, et al: Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. Circulation 101:47, 2000
11. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, et al: Power-law relationship of heart rate variability as a predictor of mortality in the elderly. Circulation 97:2031, 1998
12. Mäkikallio TH, Seppänen T, Airaksinen KEJ, et al: Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. Am J Cardiol 80:779, 1997
13. Mäkikallio TH, Høber S, Køber L, et al: Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. Am J Cardiol 83:836, 1999
14. Mäkikallio TH, Ristimäe T, Airaksinen KEJ, et al: Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. Am J Cardiol 81:27, 1998
15. Lombardi F, Sandrone G, Mortara A, et al: Linear and nonlinear dynamics of heart rate variability after acute myocardial infarction with normal and reduced left ventricular ejection fraction. Am J Cardiol 77: 1283, 1996
16. Eckmann JP, Ruelle D: Ergodic theory of chaos and strange attractors. Rew Mod Physics 57:617, 1985
17. Grassberger P, Procaccia I: Measuring the strangeness of strange attractors. Physica 9D:189, 1983
18. Skinner JE, Pratt CM, Vybiral T: A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. Am Heart J 125:731, 1993
19. Grassberger P, Procaccia I: Estimation of the Kolmogorov entropy from a chaotic signal. Phys Rew A 28:2591, 1983
20. Pincus SM, Goldberger AL: Physiologic time-series analysis: What does regularity quantify? Am J Physiol 226:H1643, 1994
21. Pincus SM, Viscarello RR: Approximate entropy: A regularity statistic for fetal heart rate analysis. Obset Gynecol 79:249, 1992
22. Woo MA, Stevenson WG, Moser DK, et al: Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. J Am Coll Cardiol 23:565, 1994
23. Huikuri HV, Seppänen T, Koistinen MJ, et al: Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. Circulation 93:1836, 1996
24. Tapanainen JM, Thomsen PE, Kober L, et al: Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. Am J Cardiol 90:347, 2002

25. Ho KKL, Moody GB, Peng CK, et al: Predicting survival in heart failure cases and controls using fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation 96:842, 1997
26. Mäkikallio TH, Huikuri HV, Hintze U, et al: Fractal analysis and time and frequency domain measures of heart rate variability as predictors of mortality in patients with heart failure. Am J Cardiol 87:178, 2001
27. Mäkikallio TH, Huikuri HV, Mäkikallio A, et al: Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. J Am Coll Cardiol 37:1395, 2001
28. Vikman S, Mäkikallio TH, Yli-Mäyry S, et al: Altered complexity and correlation properties of R-R interval dynamics before the spontaneous onset of paroxysmal atrial fibrillation. Circulation 100:2079, 1999
29. Hogue CW Jr, Domitrovich PP, Stein PK, et al: RR interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. Circulation 98:429, 1998