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Development of more erratic heart rate patterns is associated with mortality post–myocardial infarction☆

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Abstract Cardiac patients often have sinus arrhythmia of nonrespiratory origin (erratic sinus rhythm [ESR]). ESR was quantified using hourly Poincaré and power spectral heart rate variability plots from normal-to-normal interbeat intervals and hourly values of the short-term fractal scaling exponent and correlations of normal-to-normal intervals in n = 60 nonsurvivors and n = 66 randomly selected survivors in the Cardiac Arrhythmia Suppression Trial. Hours were coded (ABN) as normal (0), borderline (0.5), or ESR (1). *t* Tests compared ABN for n = 2413 paired hours at baseline and on therapy. ABN was higher in nonsurvivors (0.38 ± 0.44 vs 0.28 ± 0.40, baseline, and 0.51 ± 0.45 vs 0.34 ± 0.43, on therapy, $P < .001$). Increased ABN with treatment were greater in nonsurvivors. Normal hours at baseline (relative risk = 0.77; 095% confidence interval, 0.62-0.96, $P = .018$) and on treatment (relative risk = 0.47; 95% confidence interval, 0.39-0.58) were significantly associated with decreased mortality compared with ESR. Quantification of ESR may identify more vulnerable patients or help monitor the effects of pharmacologic treatment.

Keywords: Heart rate; Risk factor; Mortality; Post-MI; Antiarrhythmic

The analysis of heart rate variability (HRV) provides information about cardiac autonomic function. However, we have found that many older subjects and patients with cardiovascular disease have an increased beat-to-beat variability that is irregular and does not reflect underlying respiratory sinus arrhythmia.[1] We have called this erratic rhythm. The presence of erratic rhythm, which is frequently episodic, increases values for short-term HRV indices such as rMSSD (root-mean-square of successive differences of normal-to-normal [N-N] interbeat intervals in milliseconds), pNN50 (the percentage of N-N intervals >50 ms different from the previous interval), and high-frequency power (the amount of variance in N-N intervals at respiratory frequencies, ie, 0.15-0.4 Hz) that quantify beat-to-beat variability. Thus, in the presence of erratic rhythm, increased short-term HRV does not, as it does for younger people, necessarily reflect greater parasympathetic control of heart rate. A high prevalence of erratic rhythm may also explain why HRV measures that are believed to reflect parasympathetic function have relatively little predictive value for outcomes. At the same time, some "nonlinear" HRV measures such as the short-term fractal scaling exponent (DFA1) and the ratio of the axes of an ellipse fitted to the Poincaré plot (SD12) do capture the presence of erratic rhythm.[2,3] DFA1 is reduced and SD12 is increased when there is a more irregular heart rate pattern. Because erratic rhythm tends to be episodic, nonlinear HRV calculated on an hourly basis should be more sensitive to the presence of erratic rhythm than 24-hour measures. In addition, erratic rhythm can be seen visually as a relatively disorganized power spectral or Poincaré plot.

We hypothesized that patients with post–myocardial infarction (MI) who have or developed an increased degree of erratic rhythm would be at higher risk of mortality than those who do not. We tested this hypothesis in the Cardiac Arrhythmia Suppression Trial (CAST). The CAST was conducted to determine if a reduction in ventricular premature beats in association with 1 of 3 randomized antiarrhythmic therapies would improve survival in patients with post-MI. Holter recordings were obtained at baseline and after the start of antiarrhythmic therapy. To

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test our hypothesis, we used a semiquantitative method to compare the degree of erratic rhythm in baseline and posttreatment recordings in CAST patients who died during follow-up and a randomly selected comparison group of those who survived.

Materials and methods

Patient population

The goal of the CAST was to test the hypothesis that suppression of VPCs would decrease mortality after MI.[4] Patients were randomly assigned to encainide, moricizine, or flecainide, with flecainide omitted in the subgroup with the lowest left ventricular ejection fraction (LVEF <30%). Patients with significant suppression of VPCs with a particular agent were continued on that agent or placebo. More complete information concerning study design may be found in the primary end-point reports.[5-7] In April 1989, the Data and Safety Monitoring Board of the CAST recommended that the encainide and flecainide arms of the study be discontinued because of increased mortality in those arms, and CAST II was begun. Patients in CAST II were selected to be at higher risk than those in CAST I.

Pretreatment (qualifying) tapes from participants in CAST (n = 830) who had their VPCs successfully suppressed on their *first* randomly assigned antiarrhythmic treatment and were continued on that agent were selected for analysis at the Washington University School of Medicine HRV Laboratory, St Louis, Mo. All of the subjects in this cohort were also classified as having usable suppression tapes.

Subjects in the current case-control study were selected from among those with analyzed recordings using the following criteria: all of the subjects (n = 68) who died and had recordings at both baseline and suppression were included. In addition, control subjects were randomly selected from among survivors, in such a way that every 10th subject (by ID) was selected, unless that subject had died, in which case, the next person was selected. As a result, 75 comparison patients were identified for the study. Because subjects were required to have usable data on both recordings, data were analyzed from 64 of 75 comparison patients and 61 of 68 nonsurvivors. Of them, n = 47 were randomized to encainide, n = 30 to flecainide, and n = 48 to moricizine.

Clinical and demographic data

Clinical and demographic data were provided by the CAST coordinating center. Characteristics of the CAST patients and procedures for data validation have been previously reported.[6]

Analysis of Holter recordings

Tapes were analyzed on a Marquette SXP Laser Holter scanner (software version 5.8; Marquette Electronics, Milwaukee, Wis) by an experienced research Holter technician using standard Holter analysis procedures. Beat-stream files, representing the time and classification of each QRS complex, were transferred to a Sun computer (Sun Microsystems, Palo Alto, Calif), where careful HRV analyses were performed using previously reported and validated techniques.[8,9] The longest and shortest true N-N intervals were identified for each tape, and intervals outside of these limits, as well as all ectopic beats, were excluded from all calculations and plots. All intervals that resulted from blocked atrial premature beats were excluded.

Detection of erratic rhythm

The presence of erratic rhythm was identified using hourly power spectral plots of 2-minute averaged HRV, hourly Poincaré plots and hourly measures of DFA1, and the correlation coefficient between N-Ns. Each hour of each recording was categorized as normal, borderline, or erratic. Details are provided below. For an hour to be acceptable for analysis, 50% of the data had to consist of N-N interbeat intervals.

Nonlinear HRV variables and erratic rhythm

Heart rate variability variables that reflect erratic rhythm and were examined included the short-term fractal scaling exponent (DFA1) and the N-N interbeat correlation coefficient (CORR). Although SD12, the ratio of the axes of an ellipse fitted to the Poincaré plot, was also calculated, it did not provide additional information and is not considered here.

1. *DFA1.* Detrended fluctuation analysis (DFA) quantifies the fractal scaling properties of the short-term R-R interval time series. Higher values for DFA reflect a more correlated time series, whereas markedly decreased values reflect a highly random time series. The method is a modified root-mean-square analysis of random walks, which quantifies the presence or absence of fractal correlation properties, and has been validated for time series.[2,10] The root-mean-square fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the window on a log-log scale. The details of this method have been described elsewhere.[2] Fractal scaling exponents were determined on an hourly basis, for short-term (4-11 beats, DFA1). Only N-N intervals were used for this calculation.

2. *Autocorrelation coefficient with a lag of one (CORR).* The Pearson correlation between the time series of N-N intervals and the same time series offset by one beat was calculated for each hour. Although not strictly speaking a nonlinear HRV measure, increased irregularity in the heart rate time series resulted in decreased values for the interbeat correlation coefficient.

Abnormal Poincaré plots and erratic rhythm

Poincaré plots (ie, plots of each N-N interval vs the next) are a graphic representation of the organization of heart rate patterns. Normal-looking 1-hour Poincaré plots of N-N interbeat intervals are ellipsoid or mildly comet shaped, with few data points outside the ellipsoid part of the figure. The left-hand side of Fig. 1A-D shows Poincaré plots categorized as normal. When the borderline plots in Fig. 2A and B are