Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients

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BACKGROUND Abnormal heart rate turbulence (HRT) has been documented as a strong predictor of total mortality and sudden death in postinfarction patients, but data in patients with congestive heart failure (CHF) are limited.

OBJECTIVE The aim of this study was to evaluate the prognostic significance of HRT for predicting mortality in CHF patients in New York Heart Association (NYHA) class II–III.

METHODS In 651 CHF patients with sinus rhythm enrolled into the MUSIC (Muerte Subita en Insuficiencia Cardiaca) study, the standard HRT parameters turbulence onset (TO) and slope (TS), as well as HRT categories, were assessed for predicting total mortality and sudden death.

RESULTS HRT was analyzable in 607 patients, mean age 63 years (434 male), 50% of ischemic etiology. During a median follow up of 44 months, 129 patients died, 52 from sudden death. Abnormal TS and HRT category 2 (HRT2) were independently associated with increased all-cause mortality (HR: 2.10, CI: 1.41 to 3.12, $P < .001$ and HR: 2.52, CI: 1.56 to 4.05, $P < .001$; respectively), sudden death (HR: 2.25, CI: 1.13 to 4.46, $P = .021$ for HRT2), and death due to heart failure progression (HR: 4.11, CI: 1.84 to 9.19, $P < .001$ for HRT2) after adjustment for clinical covariates in multivariate analysis. The prognostic value of TS for predicting total mortality was similar in various groups dichotomized by age, gender, NYHA class, left ventricular ejection fraction, and CHF etiology. TS was found to be predictive for total mortality only in patients with QRS > 120 ms.

CONCLUSION HRT is a potent risk predictor for both heart failure and arrhythmic death in patients with class II and III CHF.

KEYWORDS: Heart rate turbulence; Congestive heart failure; Prognosis; Mortality; Sudden death.

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Introduction

Despite advancement in prevention and management of congestive heart failure (CHF), mortality remains high, even in patients with preserved or relatively preserved left ventricular ejection fraction (LVEF), who currently may account for up to 40% to 50% of CHF populations.[1–3] Sudden death accounts for about 50% to 60% of the mortality in patients in New York Heart Association (NYHA) class II–III, whereas progressive heart failure predominates in NYHA class IV.[4,5] Implantation of an implantable cardioverter-defibrillator (ICD) was shown to improve survival among patients with impaired systolic left ventricular function independently of etiology.[6–8] Recent years have brought increasing interest in heart rate dynamics in risk stratification. Monitoring heart rate behavior and response is especially important in CHF patients because early autonomic nervous system dysfunction and neurohormonal activation play a dominant role in the progression and prognosis of this disease.[9]

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Heart rate turbulence (HRT) is considered to be a vagally mediated phenomenon, noninvasively reflecting baroreflex sensitivity, the latter being frequently impaired in patients with heart failure.[10,11] Blunted HRT has been observed in patients with cardiomyopathies regardless of the underlying etiology.[12–17] Abnormal HRT has been documented as a strong predictor of total mortality and sudden death in postinfarction patients, but data on its predictive value for mortality in patients with heart failure are limited.[13–15,18–24] Therefore, we aimed to evaluate the prognostic significance of HRT for predicting total mortality and different modes of death in a large cohort of patients with CHF in NYHA class II-III.

Methods

Study population

The study population consisted of 651 patients with CHF and sinus rhythm enrolled in the MUSIC (Muerte Subita en Insuficiencia Cardiaca [Sudden Death in Heart Failure]) study, a prospective multicenter longitudinal study designed to assess risk predictors of sudden cardiac death in patients with CHF in NYHA class II-III.

Patients were consecutively enrolled in the MUSIC study at specialized heart failure clinics between April 2003 and December 2004. All had established symptomatic heart failure (NYHA class II-III) and were treated according to institutional guidelines. Patients were excluded if they had recent acute coronary syndrome (within the last 3 months) or severe valvular disease amenable to surgical repair. Patients with severe pulmonary, hepatic, or renal disease or other concomitant noncardiovascular diseases expected to reduce life expectancy to <3 years were also excluded. The study protocol was approved by institutional investigation committees, and all patients signed informed consent forms.

Clinical data

Data on demographic and clinical characteristics as well as medication were acquired at enrollment. All subjects had 12-lead electrocardiogram (ECG), echocardiography, chest radiograph, and 24-hour Holter monitoring performed at enrollment. Left ventricle diameters and LVEF were assessed by means of 2-dimensional echocardiography.

Holter recordings

Ambulatory 24-hour 3-channel ECG recordings with XYZ orthogonal leads were performed using ELA Spiderview recorders and analyzed using ELA Synescope Holter software (ELA Medical, Sorin Group, Paris, France) to evaluate the presence of ventricular arrhythmias and HRT parameters.

Heart rate turbulence analyses

For calculation of HRT parameters, ECG data were exported from the ELA system to the HRT View program, an algorithm available from the web page for noncommercial use of HRT (www.h-r-t.org). In HRT analysis, 2 numerical descriptors were estimated: turbulence onset (TO) reflecting the initial phase of sinus rhythm acceleration, and turbulence slope (TS) describing the deceleration phase. TO was defined as the percentage difference between the mean of the first 2 RR intervals after a ventricular premature beat and the 2 last sinus RR intervals before the ventricular premature beat. TS was determined as the maximum positive slope of a regression line assessed over any of 5 consecutive RR intervals within the first 20 sinus RR intervals after a ventricular premature beat. TO was calculated for all ventricular premature beats separately and then averaged, whereas TS was calculated based on an averaged local tachogram. Filtering algorithms were used to eliminate inappropriate RR intervals and ventricular premature beats with coupling intervals that were too long, or compensatory intervals that were too short. Patients having at least 1 ventricular premature beat during the 24-hour ECG recording were eligible for HRT analysis.

TO and TS were defined as abnormal according to the definition proposed by Schmidt et al[18]: TS $\leq$ 2.5 ms/RR and TO $\geq$ 0%. When using both HRT parameters simultaneously, patients were categorized as having HRT0, with both HRT parameters normal, HRT1, with 1 of 2 HRT parameters abnormal, and HRT2 when both TS and TO were abnormal, similar to other studies.[18–20] Following our previous report[12] indicating significantly altered HRT parameters in CHF patients as compared with postinfarction populations, we performed additional analyses using cutoffs based on quartile division.

Follow-up and endpoints

Follow-up visits were conducted on an outpatient basis every 6 months or according to the patient's clinical status. Patients were followed up for a median of 44 months, with total mortality as a primary and sudden death as a secondary endpoint. Information about deceased patients was obtained from medical records, patients' physicians, and family members. In each case the attempt was made to determine the nature of death. Death was defined as sudden if it was: (1) a witnessed death occurring within 60 minutes from the onset of new symptoms, unless a cause other than cardiac was obvious; (2) an unwitnessed death (<24 hours) in the absence of pre-existing progressive circulatory failure or other causes of death; or (3) a death during attempted resuscitation. Deaths caused by end-stage heart failure were defined as those occurring in hospitals as a result of refractory progressive pump failure. Endpoints were reviewed and classified by the MUSIC Study Endpoint Committee.

Statistical analysis

All continuous variables are expressed as a mean $\pm$ SD for normally distributed data and as a median for variables with nonnormal (skewed) distribution. Univariate comparisons of data between patients with and without events during follow-up were performed using a Student t-test, the Mann-Whitney test, or chi-square analysis, where appropriate.

Kaplan–Meier survival curves with log rank tests were used to evaluate the associations of HRT parameters with