Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure

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Reduced heart rate variability (HRV) is associated with poor outcome in patients with heart failure (HF). However, the data on predictive value of RR variability during atrial fibrillation (AF) are limited. Therefore, the aim of this study was to evaluate the association between ventricular response characteristics and long-term clinical outcome in the population of ambulatory patients with mild-to-moderate HF and AF at baseline. The study included 155 patients (mean age 69 ± 10 years) with AF at 20-minute Holter electrocardiographic (ECG) recordings at enrollment. HRV analysis included SDNN, rMSSD, and pNN50, whereas irregularity indexes included 2 nonlinear parameters: approximate entropy (ApEn) and Shannon entropy. After median 41 months of follow-up, 54 patients died, including 21 HF related and 16 sudden deaths. Patients with ApEn ≤1.68 (lower tertile) had 40% mortality versus 12% in others (p <0.001) at 2 years of follow-up. Only nonlinear HRV parameters (irregularity but not variability indexes) identified patients at higher risk during follow-up. Decreased ApEn ≤1.68 was an independent predictor of total mortality (hazard ratio [HR] 2.81, 95% confidence interval [CI] 1.61 to 4.89, p <0.001), sudden cardiac death (HR 3.83, 95% CI 1.31 to 11.25, p = 0.014), and HF death (HR 3.45, 95% CI 1.42 to 8.38, p = 0.006) in a multivariate Cox analysis. In conclusion, in a post hoc analysis of Muerte Subita en Insufficiencia Cardiaca study AF cohort, reduced irregularity of RR intervals during AF, likely caused by autonomic dysfunction, was an independent predictor of all-cause mortality and sudden death and HF progression in patients with mild-to-moderate HF, whereas traditional HRV indexes did not predict outcome. **(Am J Cardiol 2015;116:1071−1075)**

The irregularity of the ventricular response during atrial fibrillation (AF) is a prominent characteristic of this rhythm disturbance. The functional impact of the irregularity of the ventricular response has been addressed in several studies that quite consistently demonstrated the deteriorating effect of irregular ventricular contractions on hemodynamics.[1−3] These findings raised a question whether irregularity per se can affect the long-term prognosis in patients with AF. The methodology of heart rate variability (HRV) was originally developed for analysis of RR series affected by autonomic influence on the sinus node of patients in sinus rhythm and has shown its value for risk stratification in the settings of heart failure (HF) or after myocardial infarction.[4−6] However, the high degree of irregularity of RR intervals during AF and its dependence on the modulation of atrioventricular conduction rather than sinus node automaticity, with the consequent lack of stationary data, hampers the use of the most conventional HRV approach, that is, frequency analysis in patients with AF.[7] The objective of our research was to evaluate the association between ventricular response characteristics and long-term clinical outcome in the population of ambulatory patients with mild-to-moderate HF with AF at baseline.

Methods

This is a post hoc analysis that involved ambulatory patients with HF and AF at baseline enrolled into the Muerte Subita en Insufficiencia Cardiaca (MUSIC) study. Symptomatic patients with HF in NYHA class II and III

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See page 1075 for disclosure information.

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Table 1
Clinical characteristics of a studied population according to outcome

Variable	Survivors (N=101)	Death (N=54)	Heart Failure Death (N=21)	Sudden Cardiac Death (N=16)
Age (years)	67±11 (70)	72±8 (73)*	73±7 (72)	69±11 (72)
Gender (males)	77 (77%)	37 (69%)	14 (67%)	13 (82%)
LVEF (%)	41±15 (38)	37±17(31)	39±19 (30)	31±11 (30)*
Ischemic etiology	20 (20%)	22 (41%)*	6 (29%)	9 (56%)*
Diabetes	32 (32%)	15 (28%)	5 (27%)	5 (31%)
Hypertension	62 (62%)	30 (55%)	13 (62%)	8 (50%)
NYHA class III	24 (24%)	21 (39%)*	12 (57%)*	4 (25%)
Medications				
Beta blockers	66 (66%)	24 (44%)*	7 (33%)*	9 (56%)
Digoxin	59 (59%)	41 (76%)*	19 (90%)*	10 (63%)
Amiodaron	18 (18%)	5 (9%)	3 (14%)	2 (13%)
ACE inhibitors/ARB	88 (88%)	39 (74%)	15 (65%)*	14 (88%)
Diuretics	90 (90%)	48 (89%)	20 (95%)	12 (81%)
Anticoagulants	96 (96%)	51 (94%)	20 (95%)	14 (88%)
Spironol	38 (38%)	29 (54%)	11 (52%)	9 (56%)
Statins	26 (26%)	15 (30%)	5 (25%)	7 (45%)
Heart rate variability and irregularity				
mRR	830±180 (811)	875±206 (832)	806±193 (803)	966±231(997)*
SDNN	193±65 (180)	180±69 (165)	160±55 (149)*	200±72 (204)
pNN20	91±5 (91)	88±7 (90)	86±9 (89)*	90±7 (92)
pNN50	79±8 (80)	75±13 (77)	72±13 (76)*	78±13 (81)
pNN70	72±10 (73)	67±15 (70)	64±15 (68)*	71±15 (75)
rMSSD	266±92 (248)	240±96 (224)	211±80 (199)*	267±100 (261)
ApEn	1.711±0.156 (1.74)	1.634±0.171 (1.665)*	1.626±0.185 (1.650)*	1.586±0.199 (1.615)*
Shannon entropy	6.35±1.44 (6.77)	5.74±1.86 (6.53)*	6.27±1.51 (6.69)	4.67±2.43 (5.70)*

Data are given as mean ± SD (median) for continuous variables or as number (percentage) for categorized variables.
* p value <0.05.

with either depressed or preserved left ventricular ejection fraction (LVEF) were enrolled at outpatient heart failure units. Detailed protocol of the study is described elsewhere.[8] The study protocol was approved by institutional investigation committees.

During the study, patients were followed every 6 months on outpatient basis with a primary end point defined as total mortality. MUSIC Study Endpoints Committee classified mode of death into cardiac and noncardiac. Cardiac deaths were classified either as sudden or due to HF progression. 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 within 24 hours of symptoms onset in the absence of pre-existing progressive HF or other causes of death, or (3) a death during attempted resuscitation. Deaths due to end-stage HF were defined as occurring in hospitals as a result of refractory HF.

At enrollment, all subjects had 24-hour ambulatory ECG recorded using SpiderView recorders (ELA Medical, Sorin Group, Paris, France). During the initial 20 minutes, electrocardiogram was recorded with 1,000-Hz resolution while patients were resting in supine position. High-resolution ECG recordings were available in 169 patients with AF. Fourteen recordings were excluded from this analysis because of poor quality. For analysis of HRV and irregularity, annotated RR series from 20-minute ECG recordings were exported and analyzed using MATLAB R2008a (The MathWorks, Natick, MA). Variability parameters included the mean (mRR) and the standard deviation (SDNN) of all normal RR intervals, the root of the mean squared differences of successive RR intervals (rMSSD) and the percentage of interval differences of successive RR intervals >50 ms (pNN50). Irregularity parameters included 2 nonlinear parameters, namely the Shannon and the approximate entropy (ApEn). The Shannon entropy is a measure of the uncertainty contained in a series.[9] ApEn is a regularity statistic quantifying the unpredictability of fluctuations in a series and reflects the likelihood that similar patterns of observations will not be followed by additional similar observations.[10] A regular and predictable series has relatively small Shannon and ApEn; a more complex process has higher Shannon and ApEn.

The *t* test, Mann-Whitney test, or chi-square analysis were used for univariable comparisons of data between groups. To evaluate the correlation between HRV parameters and clinical covariates, Pearson or Spearman tests were used, where appropriate. Cumulative probability of survival was estimated according to the Kaplan-Meier method with comparisons made using the log-rank tests. The Cox proportional hazards regression model was used in the prediction of the specified end points. A p value <0.05 was considered statistically significant. Data were analyzed using SPSS, version 20 (SPSS Inc, Chicago, Illinois).

Results

The studied population comprised 155 patients (114 men), mean age 69 ± 10 years, with HF in NYHA class II