Prognostic role of heart rate variability in patients with idiopathic dilated cardiomyopathy

Gaetano A. Lanza, Maria Grazia Bendini, Anselma Intini, Giuseppe De Martino, Marco Galeazzi, Vincenzo Guido, Alfonso Sestito

Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

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Idiopathic dilated cardiomyopathy; Heart rate variability; Prognosis.

Background. **The aim of this study was to investigate whether heart rate variability may predict the outcome in patients with idiopathic dilated cardiomyopathy.**

Methods. **Time-domain and frequency-domain heart rate variability was analyzed on 24-hour Holter recordings of 56 patients with idiopathic dilated cardiomyopathy (70% males, mean age 49 – 16 years; left ventricular ejection fraction 28 – 6%).**

Results. **There were 8 cardiac deaths (14.3%) and 11 arrhythmic events (19.6%, either sudden death or sustained ventricular tachycardia) at a follow-up of 18.5 months (range 3-50 months). Furthermore, 6 patients were included in the list for cardiac transplantation, leading to a prevalence of total cardiac events of 37.5% (21 patients). All time-domain and most frequency-domain heart rate variability parameters did not show any significant relationship with the end points. However, a low frequency to high frequency (LF/HF) ratio < 1.2 was associated with cardiac death (relative risk-RR 6.8, $p < 0.03$), arrhythmic events (RR 11.0, $p < 0.004$), and total cardiac events (RR 4.8, $p < 0.002$). On the multivariate Cox analysis, no variable showed an independent association with cardiac death, but an LF/HF ratio < 1.2 was the only variable independently predictive of arrhythmic events (RR 8.2, $p < 0.02$), and the most powerful predictor of total cardiac events (RR 3.8, $p < 0.009$).**

Conclusions. **Our data show that, in patients with idiopathic dilated cardiomyopathy, a low LF/HF ratio, as assessed on 24-hour Holter recordings, is a powerful predictor of cardiac events.**

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Address:

Dr. Gaetano A. Lanza

Istituto di Cardiologia
Universit Cattolica del Sacro Cuore
Policlinico Agostino Gemelli
Largo Agostino Gemelli, 8
00168 Roma

A low variability of RR intervals (heart rate variability-HRV) has been demonstrated to be a predictor of mortality in patients recovering from an acute myocardial infarction[1-7]. Other studies have shown that HRV is significantly impaired in patients affected by left ventricular heart failure[8-17]. However, there are limited data concerning the ability of HRV analysis to predict the occurrence of cardiac events in this latter group of patients. Moreover, patients with different causes of the impairment of cardiac pump function were usually included in previous studies[18-21], although it is not clear whether the predictive prognostic value of HRV is similar in patients with different etiopathogenesis of heart failure. Indeed, several other variables, including ventricular arrhythmias, late potentials, and baroreflex sensitivity, have previously been shown not to have the same prognostic impact in patients with different causes of heart failure, mainly ischemic or idiopathic[3,22-33].

The present study was undertaken to specifically investigate whether HRV analysis, in the time domain, frequency domain, or both, may be useful in the risk stratification of patients with a documented impairment of systolic left ventricular function and a final diagnosis of idiopathic dilated cardiomyopathy.

Methods

Patients. One hundred ten consecutive patients, admitted to our Cardiology Division because of signs or symptoms of systolic left ventricular dysfunction and in whom ischemic heart disease and other secondary causes of heart failure were excluded by full clinical and noninvasive and invasive (including coronary angiography) diagnostic investigation, were considered for this study.

Patients were included only if they had left ventricular ejection fraction (LVEF) < 40%, as assessed by both echocardiography and left ventricular angiography. Patients were excluded from the study if they had one or more of the following: LVEF 40%; atrial fibrillation; frequent premature supraventricular ectopic beats; diabetes or other dis-

eases known to affect the autonomic nervous system; pacemaker rhythm; Holter recordings lasting < 20 hours or with technical deficiencies resulting in an unreliable analysis; inability to follow up the patient.

The final study population consisted of 56 patients (51% of the total). The following variables were recorded for each patient: age and gender; NYHA functional class; LVEF; treatment at the time of Holter monitoring. Therapy was not standardized and was at the total discretion of the attending physicians.

Holter monitoring and heart rate variability analysis. All patients underwent a 24-hour Holter recording with 2-channel real-time tape recorders (Oxford Medilog 4500), monitoring the bipolar chest leads CM5 and CM1. Holter tapes were analyzed using an Oxford Medilog Excel 2.0 device. For each patient the total number of premature ventricular beats, and the number of episodes of nonsustained ventricular tachycardia (3 consecutive premature ventricular beats with a rate 100 b/min) were obtained.

HRV was assessed over the entire 24 hours, after careful revision of the electrocardiogram and editing of beats, when indicated. Time-domain HRV variables included: mean RR interval (RR); standard deviation of all RR intervals (SDNN); mean of the standard deviations of all RR intervals for all 5-min segments (SDNNi); standard deviation of the mean RR intervals for all 5-min segments (SDANN); the square root of the mean squared differences of successive RR intervals (RMSSD); percent of differences between adjacent RR intervals > 50 ms (pNN50).

In the frequency domain, HRV was assessed by a fast Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz, using the version 7.0 Oxford HRV analysis package. The amplitude of the following frequency-domain HRV variables was obtained: total spectrum (0-0.50 Hz), ultra-low frequency (ULF, 0.0000-0.0033 Hz), very-low frequency (VLF, 0.0033-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.40 Hz). Finally, the LF/HF ratio, which was considered as an index of sympatho-vagal balance in previous studies[34-36], was also calculated.

Follow-up. The follow-up of patients was done by outpatient clinic visit or by telephone. In the case of events, detailed information was obtained by the patient or by his/her relatives and/or from the private physician and/or clinical recordings.

The following end points were considered for the study: 1) cardiac death, defined as death caused by progressive heart failure or sudden cardiac death, with this latter defined as either instantaneous, unexpected death, or death occurring within 1 hour of symptom onset; 2) arrhythmic events, defined as the occurrence of either sudden death or documented sustained ventricular tachycardia, defined as hemodynamically unstable ventricular tachycardia or ventricular tachycardia lasting 30 s; 3) total cardiac events, which included either cardiac death or sustained ventricular tachycardia or a worsening of heart failure, leading to the inclusion on a list for cardiac transplantation.

Statistical analysis. Comparisons between groups of continuous variables were done by unpaired Student s t-test or Mann-Whitney U-test, as indicated. Proportions were compared by Fisher exact test. The association of individual variables with end points was assessed by univariate Cox regression analysis. To this aim, the following continuous variables were dichotomized according to predefinite cut-points: 1) age (> 60 vs < 60 years); 2) NYHA functional class I-II vs III-IV; 3) number of premature ventricular beats per hour (10 vs < 10); 4) LVEF (30 vs < 30%).

Furthermore, we also looked for cut-points that maximized the association of HRV variables with the end point of arrhythmic events, according to the highest β coefficient obtained on the univariate Cox regression model[2,7]. Arrhythmic events were chosen as a reference for dichotomization, as statistical analysis showed a better association of HRV variables with this than with the other end points. However, substantially identical cut-points were obtained when other clinical end points were considered. Survival curves were constructed by Kaplan-Meier method and compared by log-rank test. The independent prognostic value of variables was assessed by multivariate stepwise Cox proportional hazard regression. Only variables with p 0.1 on univariate analysis were entered in the multivariate model and variables were maintained in the model only if they reached statistical significance.

Sensitivity, specificity, positive and negative predictive values were calculated using standard arithmetic formulae. Data are reported as mean – SD. A $p < 0.05$ was considered as statistically significant.

Results

General findings and follow-up. The main clinical characteristics of the patients are summarized in table I. The mean age of patients was 49 – 16 years and 70% of them were males. LVEF was 28 – 6%, being < 30% in 31 (55%). A left bundle branch block was present in 34 patients and a right bundle branch block in 1. Frequent premature ventricular beats (10/hr) on Holter monitoring were found in 42 (75%) patients, with episodes of nonsustained ventricular tachycardia being detected in 30 (54%).

There were 8 deaths (14.3%), all of cardiac origin (4 sudden), in a median follow-up time of 18.5 months (range 3-50 months). Arrhythmic events occurred in 11 patients (19.6%), 4 of whom experienced sudden death and 7 documented sustained ventricular tachycardia, 6 of these requiring automatic implantable defibrillator. Six patients in this follow-up period were included in the list for cardiac transplantation, leading to a prevalence of to-

Table I. Clinical characteristics of the patients.

No. patients	56
Age (years)	49 – 16
Male gender	39 (70%)
Duration of disease (months)	24 – 38
NYHA functional class	
I-II	38 (68%)
III-IV	18 (32%)
LBBB	34 (61%)
LVEF (average, %)	28 – 6
LVEF < 30%	31 (55%)
PVBs 10/hr	42 (75%)
NSVT	30 (54%)
Drug therapy	
Digoxin	36
Diuretics	44
ACE-inhibitors	40
Beta-blockers	5
Ca^{2+}-antagonists	1
Nitrates	20
Aspirin	20
Amiodarone	15

ACE = angiotensin-converting enzyme; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVBs = premature ventricular beats.

tal cardiac events of 37.5% (21 patients). Five of these 6 patients had actually undergone cardiac transplantation at the time of the last follow-up.

Cardiac death. Univariate predictors of each end point are shown in table II. The only clinical variable which tended to be associated with cardiac death was LVEF < 30% (p = 0.05).

HRV variables did not differ significantly in patients with or without cardiac death, although frequency-domain parameters tended to be lower in patients who died (Table III). The LF/HF ratio, however, was significantly lower (p < 0.05) in patients with cardiac death (Table III). In particular, an LF/HF ratio < 1.2 was associated with a 6.8-fold increase of the risk of death (95% confidence interval-CI 1.3-36.6, p < 0.03), with survival curves of patients with LF/HF ratio < 1.2 and those with LF/HF ratio 1.2 showing a highly significant statistical difference (p < 0.006; Fig. 1). No other HRV variable showed cut-points which could significantly discriminate patients with or without cardiac death.

Sensitivity, specificity, positive and negative predictive values of LF/HF ratio < 1.2 for cardiac death were 0.62, 0.75, 0.29, and 0.92, respectively.

Arrhythmic events. The only clinical univariate predictor of arrhythmic events was age > 60 years (p < 0.02; Table II). Furthermore, arrhythmic events occurred only in male patients. Both time-domain and frequency-domain HRV variables did not differ significantly in patients with or without arrhythmic events, but the LF/HF ratio was lower in patients with this end point (1.1 – 0.4 vs 1.5 – 0.5, p < 0.005; Table III).

In particular, an LF/HF ratio < 1.2 was associated with

Table II. Significant univariate predictors of cardiac events.

Variable	Relative risk (95% CI)	p
Cardiac death		
LVEF < 30%	9.0 (1.0-81.4)	0.05
LF/HF ratio < 1.2	6.8 (1.3-36.6)	< 0.03
Arrhythmic events*		
Age > 60 years	4.9 (1.5-16.4)	< 0.02
LF/HF ratio < 1.2	11.0 (2.3-53.5)	< 0.004
Total events		
Male gender	3.7 (1.1-12.2)	< 0.05
NSVT	3.3 (1.2-9.0)	< 0.03
LF/HF ratio < 1.2	4.8 (1.8-12.5)	< 0.002

CI = confidence interval; HF = high frequency; LF = low frequency; NSVT = nonsustained ventricular tachycardia. * all arrhythmic events occurred in male patients.

Table III. Average values of heart rate variability parameters in patients with or without cardiac events.

	Cardiac death		Arrhythmic events		Total events	
	Yes	No	Yes	No	Yes	No
RR	797 – 100	795 – 154	852 – 101	781 – 154	805 – 146	789 – 149
SDNN	121 – 49	114 – 49	121 – 41	114 – 50	113 – 51	117 – 48
SDNNi	41.5 – 12	52.3 – 24	47.2 – 20	51.6 – 23.5	47.1 – 22	52.9 – 23
SDANN	118 – 50	102 – 48	110 – 43.5	103 – 50	101 – 50.5	106 – 48
RMSSD	35.8 – 14	42.9 – 33	49.2 – 40	40.1 – 29	44.7 – 34	40.2 – 30
pNN50	5.9 – 7.5	6.7 – 10.5	6.4 – 7.5	6.6 – 10.7	5.7 – 8.3	7.1 – 11.1
TPF	42.1 – 15	58.7 – 31	50.9 – 23	57.7 – 32	49.5 – 25	60.4 – 32
ULF	16.7 – 10	22.1 – 21	19.8 – 14	21.7 – 22	19.4 – 14	22.5 – 23
VLF	31.2 – 12	43.6 – 20.5	35.5 – 16	43.4 – 21	35.7 – 19	45.5 – 20
LF	15.6 – 7	22.7 – 13	16.7 – 7	22.9 – 14	17.1 – 9*	24.5 – 14
HF	13.6 – 5	16.2 – 11	15.7 – 7	15.8 – 11	15.4 – 8	16.1 – 12
LF/HF ratio	1.2 – 0.5*	1.5 – 0.5	1.1 – 0.4**	1.5 – 0.5	1.2 – 0.4**	1.6 – 0.4

See text (Methods) for definition of heart rate variability variables. * p < 0.05; ** p < 0.005.

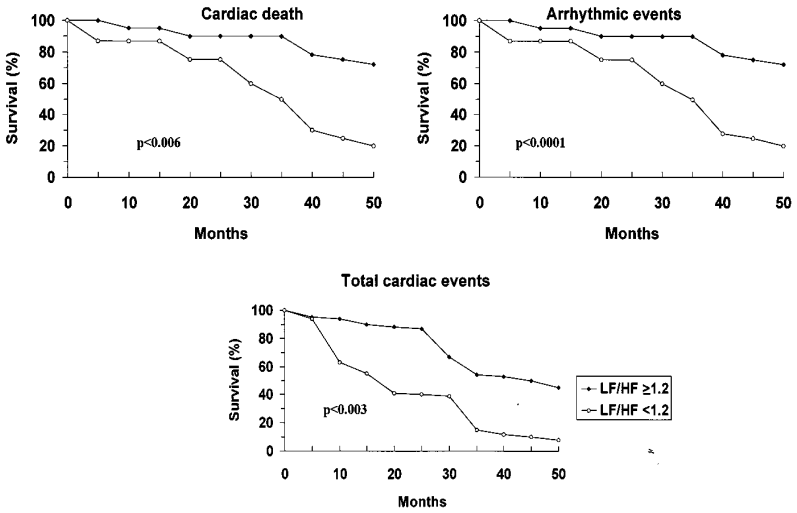

Figure 1. *Kaplan-Meier event-free survival curves for end point occurrence and log-rank test results for curve differences between patients with a low frequency/high frequency (LF/HF) ratio 1.2 or < 1.2.*

an 11-fold increase of the risk of arrhythmic events on univariate analysis (95% CI 2.3-53.5, p < 0.004), and survival curves of patients with LF/HF ratio < 1.2 and those with LF/HF ratio 1.2 showed a highly significant statistical difference (p < 0.0001; Fig. 1) for this end point. No other HRV variable showed cut-points which could significantly discriminate patients with or without arrhythmic events.

Sensitivity, specificity, positive and negative predictive values of LF/HF ratio < 1.2 for arrhythmic events were 0.73, 0.80, 0.47, and 0.92, respectively.

Total cardiac events. Clinical univariate predictors of total cardiac events included male sex (p < 0.05), and nonsustained ventricular tachycardia on Holter monitoring (p < 0.03, Table II). As for the other end points, time-domain HRV variables did not differ significantly in patients with or without events. Conversely, the LF/HF ratio (1.12 – 0.4 vs 1.6 – 0.4, p < 0.005) and LF amplitude (17.1 – 9 vs 24.5 – 14 ms, p < 0.05) were significantly lower in patients with, compared to those without, total events, with VLF also showing a similar trend (35.7 – 19 vs 45.5 – 20, p < 0.08; Table III).

The LF/HF ratio, however, was the only HRV parameter showing a significant association with arrhythmic events on the univariate Cox analysis. An LF/HF ratio < 1.2 was associated with a 4.8-fold increase of the risk of total events (95% CI 1.8-12.5, p < 0.002), and survival curves of patients with LF/HF ratio < 1.2 and those with LF/HF ratio 1.2 showed a highly significant statistical difference (p < 0.003; Fig. 1). No other HRV variable showed cut-points which could significantly discriminate between patients with or without total cardiac events.

Sensitivity, specificity, positive and negative predictive values of LF/HF ratio < 1.2 for total cardiac events were 0.57, 0.86, 0.71, and 0.77, respectively.

Multivariate analysis. The results of the multivariate Cox proportional hazard regression analysis are summarized in table IV. Sex was not included in the multivariate analysis for arrhythmic events, as all patients with this end point were males. No variable showed significant independent predictive association with cardiac death. Conversely, LF/HF ratio < 1.2 was the only variable independently predictive of arrhythmic events (RR 8.2, p < 0.02), and it was also the most powerful predictor of total cardiac events (RR 3.8, p < 0.009), with the male gender being the only other variable with a significant borderline association with this end point (RR 3.5, p = 0.05).

Discussion

Table IV. Results of the multivariate analysis.

Variable	Relative risk (95% CI)	p
Cardiac death		
LVEF < 30%	4.0 (0.7-22.8)	0.11
LF/HF ratio < 1.2	5.8 (0.6-59.1)	0.13
Arrhythmic events		
LF/HF ratio < 1.2	8.2 (1.6-43.4)	< 0.02
Total events		
LF/HF ratio < 1.2	3.8 (1.4-9.9)	< 0.009
Male gender	3.5 (1.0-12.4)	0.05
NSVT	2.5 (0.9-7.1)	0.09

Abbreviations as in tables I and II.

In this study we specifically investigated the role of most time-domain and frequency-domain HRV variables in predicting survival in patients with idiopathic dilated cardiomyopathy. Although several previous studies evaluated the prognostic role of HRV in patients with heart failure, most included patients with different etiologies of the disease[18-21]. In our opinion, the selection of a homogeneous population of patients with idiopathic dilated cardiomyopathy may be clinically important. Indeed, while left ventricular failure is a hominous sign of the outcome independently of its cause, the predictive power of prognostic variables may not necessarily be the same in patients with different causes of heart failure. In fact, this has already been shown for several prognostic indicators, including ventricular arrhythmias, late potentials and baroreflex sensitivity, all of which have been consistently found to be of relevant prognostic value in ischemic heart disease[22-27], but not in patients with idiopathic dilated cardiomyopathy[27-33].

In this study, time-domain and most frequency-domain variables did not show any statistically significant differences between patients with or without cardiac end points in the follow-up. The LF/HF ratio, however, gave valuable prognostic information in these patients, being significantly lower in patients developing cardiac events. Specifically, an LF/HF ratio < 1.2 allowed us to identify a subgroup of patients at a particularly increased risk of events.

Heart rate variability in chronic heart failure and idiopathic dilated cardiomyopathy. Several previous studies have shown that HRV is lower in patients with an impairment of left ventricular function[8-17]. In particular, patients with severe systolic left ventricular dysfunction were shown to have a considerable reduction in LF power and a decreased LF/HF ratio[8-12].

It is not completely clear, however, whether an impairment of HRV may further discriminate patients with a worse prognosis even in this high-risk group of patients. Several previous studies have shown that both time-domain and frequency-domain HRV variables are able to predict the clinical outcome in patients with heart failure. However, most of these studies included heterogeneous groups of patients[18-21]. In the largest prospective study on the prognostic role of HRV in patients with symptoms/signs of chronic heart failure[20], for example, a relevant number of patients had normal systolic function, with LVEF being > 50%, and also > 60% (Fig. 1 of that study)[20]. Moreover, only a few, predominantly time-domain, HRV variables were evaluated in most of the previous studies[18-21].

However, in some studies, which specifically assessed the prognostic value of HRV in patients with idiopathic dilated cardiomyopathy, the few patients with fatal cardiac events seemed to have a more impressive LF power reduction, although survival analysis could not be done due to the small number of cases[9,11,12]. In fact, although a relationship of low SDNN with progressive heart failure was reported by Yi et al.[37], only one study, to our knowledge, specifically investigated the association of HRV with survival in patients with idiopathic dilated cardiomyopathy[38]. In this study, Fauchier et al. evaluated two time-domain HRV parameters in 93 patients with a diagnosis of idiopathic dilated cardiomyopathy. They found that an SDNN < 100 ms was significantly associated with total cardiac events (cardiac death, heart transplantation, cardiomyoplasty), but not with cardiac death. Furthermore, no significant predictivity could be found for RMSSD[38].

In a subsequent study, probably including most of the same patients, Fauchier et al.[39] reported that a low SDNN was also an independent predictor of sudden death and arrhythmic events in patients with idiopathic dilated cardiomyopathy, whereas frequency-domain variables (VLF, LF and HF) were not predictive of these end points. On the other hand, Hoffmann et al.[40] did not find a significant association between HRV variables and arrhythmic events, although some time-domain parameters showed a tendency towards statistical significance.

In contrast with these previous data, we have found that frequency-domain rather than time-domain HRV analysis can be particularly useful in the risk stratification of patients with idiopathic dilated cardiomyopathy. Indeed, lower LF/HF ratio values were associated with a higher occurrence of cardiac events in the follow-up. In particular, an LF/HF ratio < 1.2 had a 6.8-fold risk of cardiac death, and an 11-fold risk of arrhythmic events. Most interestingly, this was largely independent of LVEF and other potential prognostic variables. Furthermore, there was a tendency for several frequency-domain HRV variables, in particular VLF and LF, to be associated with cardiac events.

The reasons for the different results between previous studies and ours is not clear, but likely include a different definition of idiopathic dilated cardiomyopathy (several patients of Fauchier s studies had a possible alcoholic, rather than idiopathic, cardiomyopathy)[38], methods of HRV analysis, drug treatment, and end points[38-40].

Our results may be of particular value as the LF/HF ratio is the first parameter showing such a strong predictive power for cardiac events in patients with idiopathic dilated cardiomyopathy. Indeed, although in some studies both clinical and laboratory[27-33,41-46] variables have been reported to influence the outcome in patients with idiopathic dilated cardiomyopathy, their predictive value is quite low[47]. In fact, our study confirms the limited prognostic role of several clinical (e.g., age, NYHA functional class, history of hypertension or diabetes) and laboratory (e.g., LVEF, ventricular arrhythmias) parameters in these patients.

According to our data, a low LF/HF ratio in patients with idiopathic dilated cardiomyopathy should lead to a more aggressive treatment and stricter clinical observation. Whether an increase in LF/HF ratio with treatment

may reverse the worse prognosis in these patients should be investigated in future studies.

Pathophysiologic implications. Power in the LF band has been demonstrated to be largely influenced by adrenergic activity[34-36,48,49], whereas, at the opposite, the HF band has been correlated with vagal activity[48,50] and the LF/HF ratio has been often believed to reflect sympathovagal balance[34-36,51]. However, the LF component of power spectrum of HRV appears to be significantly influenced by mechanisms other than sympathetic activation. Moreover, the considerable reduction of LF in patients with left ventricular dysfunction, which is often associated with increased adrenergic activity, indicates that HRV in this frequency band cannot always be taken as a reliable index of adrenergic tone in these patients. This may be particularly true when, as in our study, spectral analysis is performed on 24-hour Holter recordings, rather than on short-term RR interval recordings. Indeed, in long-term, uncontrolled recordings, rhythmical RR fluctuations are more likely to be influenced by non-neural components. Furthermore, it should be considered that also an impairment in sinus node response to sympathetic activity could contribute to the reduction of LF in patients with idiopathic dilated cardiomyopathy, who may have structural and functional alterations of the primary cardiac pacemaker[52,53].

Limitations of the study. Owing to the careful selection of patients, in this single-center study we were able to include only a limited number of patients with idiopathic dilated cardiomyopathy. This may have hampered the possibility to detect significant differences in most HRV variables between patients with or without events. However, the demonstration that the LF/HF ratio is a predictor of events, in spite of the low number of patients, suggests that this HRV variable may actually be the most useful one in the risk stratification of patients with idiopathic dilated cardiomyopathy.

The assessment of HRV was made under standard drug therapy in our patients. This may have influenced HRV measures, as several drugs have been found to modify HRV[54-56]. However, it would have been unethical to withdraw treatment in most of these patients. Furthermore, we think that it can be more useful to evaluate HRV while patients are taking their usual drug therapy (rather than off treatment), since this latter could influence prognosis by improving HRV.

In this study frequency-domain HRV was measured in ms rather than in ms^2. This did not obviously have any effects on statistical results. The analysis of data, using ms^2 as a measure unit, led to a prognostic discriminating cut-point for LF/HF ratio of 1.5.

Finally, in this study we considered as arrhythmic events the occurrence of either sudden death or sustained ventricular tachycardia, and this may not be completely appropriate, as sudden death may be consequent to bradyarrhythmias rather than tachyarrhythmias in some cases. However, although bradyarrhythmias have been reported to be a frequent cause of sudden death in hospitalized patients with advanced heart failure[57], ventricular tachycardia or fibrillation remains the most frequent mode of sudden death in patients dying out of hospital[58], as was the case in our patients. Furthermore, our patients with sustained ventricular tachycardia were actually at a very high risk of sudden death, as indicated by the fact that 5 out of 6 of them underwent cardioverter-defibrillator implantation, due to inducibility of ventricular fibrillation or fast sustained ventricular tachycardia on electrophysiologic study.

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