

ORIGINAL ARTICLES

Baseline Heart Rate Variability Predicts Clinical Events in Heart Failure Patients Implanted with Cardiac Resynchronization Therapy: Validation by Means of Related Complexity Index

Giulio Molon, M.D.,* Francesco Solimene, M.D.,† Donato Melissano, M.D.,‡ Antonio Curnis, M.D.,§ Giuseppina Belotti, M.D.,# Natale Marrazzo, M.D.,† Jacek Marczyk, B.S.,¶ Francesco Accardi, B.S.,** Giovanni Raciti, B.S.,** and Paolo Zecchi, M.D.††

From the *Department of Cardiology, S. Cuore Hospital, Negrar, Verona, Italy; †Casa di Cura Montevergine, Mercogliano, Avellino, Italy; ‡P.O. di Casarano, Casarano, Lecce, Italy; §A.O. Spedali Civili, Brescia, Italy; #O. di Treviglio – Caravaggio, Treviglio, Bergamo, Italy; ¶Ontomed, Ann Arbor, MI; **Boston Scientific, Segrate, Milan, Italy; and ††Cattolica University del Sacro Cuore – Policlinico A. Gemelli, Roma, Italy

Background: Studies on the physiology of the cardiovascular system suggest that generation of the heart rate (HR) signal is governed by nonlinear dynamics. Linear and nonlinear indices of HR variability (HRV) have been shown to predict outcome in heart failure (HF). Aim of the present study is to assess if a HR-related complexity predicts adverse clinical and cardiovascular events at 1 year in patients implanted with cardiac resynchronization therapy (CRT).

Methods: In sixty patients implanted with CRT (Renewal), 24-hour HR data were retrieved at patient discharge and 1-year follow-up. A set of linear indices of HRV were considered: mean HR, standard deviation of normal beat to normal beat (SDANN), and HR footprint. Two novel nonlinear indices were calculated by means of a specific algorithm (OntoSpace): HR-complexity (HR-Co) and HR-entropy (HR-En). Predictors of adverse clinical outcome (functional class deterioration or major hospitalizations for cardiovascular causes or all-cause mortality) and of HRV recovery were sought by means of multivariate analysis.

Results: HR-Co and HR-En were found to be highly correlated with the other traditional indices of HRV. Lower baseline values of complexity were associated with adverse clinical outcomes (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.54–0.95; $P < 0.02$).

Conclusion: Complexity and entropy indices, calculated from 24-hour normal beat to normal beat (RR) intervals well represent patient's autonomic function. In this limited set of data, HF patients with lower baseline complexity-related indices, representing a more compromised autonomic function, present worse clinical outcome at 1-year follow-up.

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biventricular pacing/defibrillation; heart rate variability

It is known that physiologic systems, both in their healthy and diseased condition, operate under unstable conditions and that nonlinear dynamics underlay the generation of most biologic signals.^{1,2} Among these signals, the analysis of heart rate (HR) and its HR variability (HRV) have become

important and widely used means for assessing cardiovascular autonomic regulation. HRV impairment is associated with many cardiovascular diseases, including ischemic disease^{3,4} and heart failure (HF),^{5–7} and has been found to have predictive value of adverse outcome. Traditional time and

Address for correspondence: G. Molon, M.D., Department of Cardiology, Sacro Cuore Hospital, via Sempredoni 5, 37024 Negrar, Verona, Italy. Fax: +390457500480; E-mail: giulio.molon@sacrocuore.it

frequency parameters as well as novel methods based on nonlinear dynamics have shown to provide prognostic information in selected patients.⁸⁻¹³ Recently, controlled clinical trials have demonstrated that cardiac resynchronization therapy (CRT) is a proven treatment for selected patients with HF conduction disturbances and ventricular dyssynchrony.^{14,15} The algorithms included in CRT devices and the increased storage capabilities, allow continuous acquisition of beat-to-beat information on heart rate, enabling additional possibilities for real-time, and offline processing of HRV data.^{16,17} These algorithms, essentially based on traditional time-domain analysis, have been proven to be useful to track HRV evolution^{18,19} and to carry prognostic information on patient outcomes.^{20,21} The value of specific algorithms based on nonlinear indices that process HR-related information in CRT devices has not been assessed yet. Recently, developed measures of complexity and entropy,²² which analyze the structure of information underlying a considered dataset, establish an innovative means of characterizing generic dynamical systems, including biologic signals. This novel measurement may carry prog-

nostic information in the context of cardiovascular diseases.

Objectives of the present study were (1) to evaluate the association between novel nonlinear and traditional linear indices, calculated from RR intervals to assess the autonomic function, (2) to assess their evolution over time in the selected sample, and (3) to evaluate their predictive value for adverse clinical outcomes in patients implanted with CRT at 1-year follow-up.

METHODS

Patients implanted with a CRT device including enhanced HRV diagnostics (Renewal, Boston Scientific, Natick, MA, USA) were considered eligible for the study. The device included the following information, stored on a daily basis: mean HR, the standard deviation of averages of intrinsic RR intervals (SDANN) calculated in 288 5-minute segments, and the footprint area. Footprint is a graphical rendering of the likelihood of a particular beat-to-beat HR change occurring at each intrinsic sinus rate during a 24-hour period (Fig. 1). The footprint area is the normalized size of the two-dimensional plot of RR

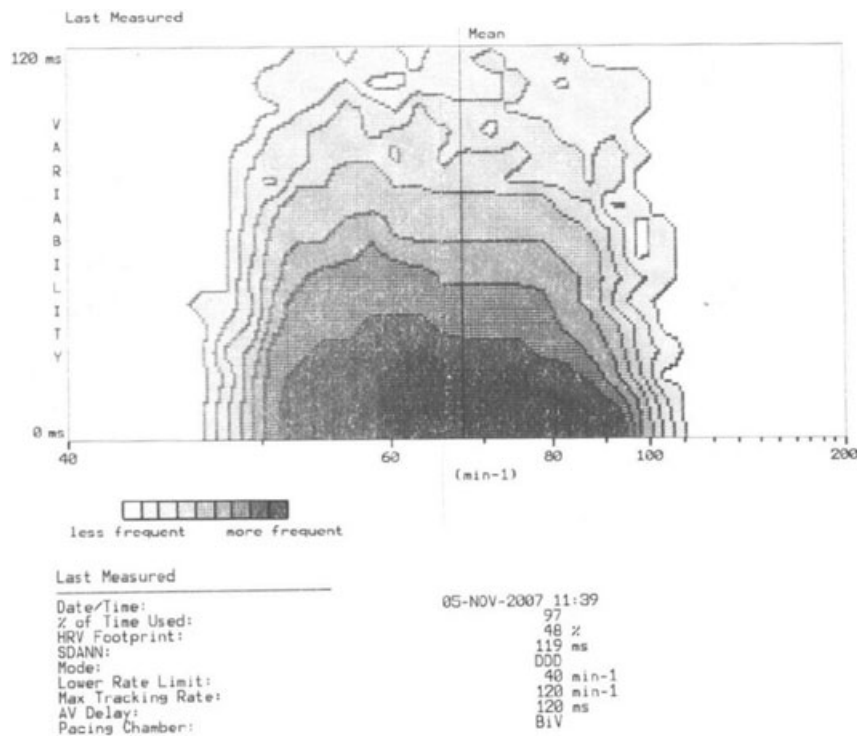


Figure 1. Heart rate-related parameters stored into a CRT device (Renewal, Boston Scientific), including SDANN and footprint.

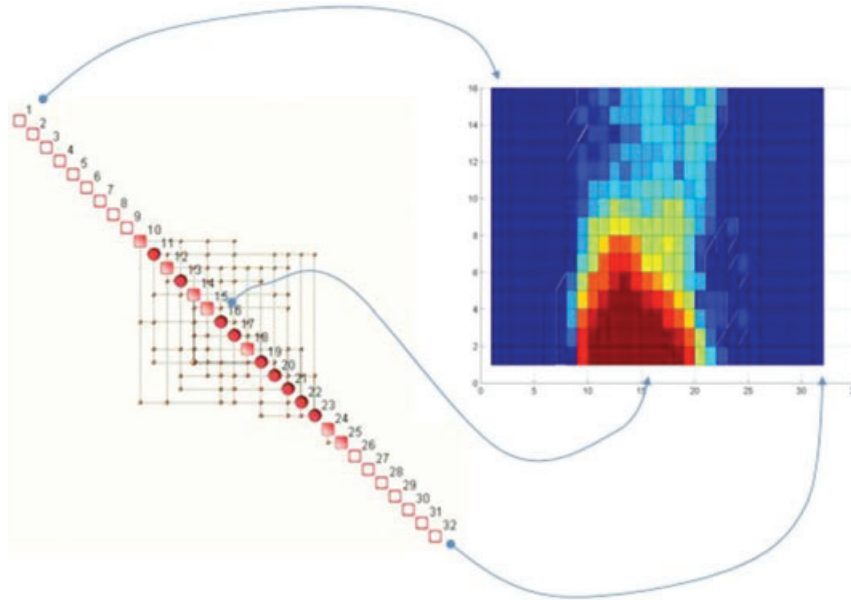


Figure 2. Correspondence between System Map variables (1–32) and HRV diagram columns.

interval variability versus HR. HRV footprint provides a graphical representation of several variables including frequency, day-to-day rate variability, maximum, minimum, and mean HR. These indices, embedded into device diagnostics, represent traditional linear parameters used to assess autonomic function and its evolution over time in patients implanted with CRT. Their prognostic value has been recently assessed in large groups of HF patients who received CRT.^{18,20,21} In addition, HR data retrieved from the footprint image (data points of the footprint plot) both at baseline and 1-year follow-up were retrieved from device memory and processed with OntoSpace (Ontomed S.r.l., Ann Arbor, MI, USA) in order to obtain the following nonlinear indices: complexity (HR-Co) and entropy (HR-En). The HR-Co and HR-En indices may be regarded as a measure of the amount of “structured information” in the footprint image itself. The process of HRV diagram complexity quantification proceeds as follows. The image is “quantized” into pixels. The size of pixels is such that it corresponds to the image discretization as stored in the device’s memory, that is, $16 \times 32 = 512$. The resulting 16×32 matrix is populated with integer entries, ranging from 0 to 15, corresponding to the color of each pixel. The matrix is processed using OntoSpace, resulting in the so-called System Map, an example of which is depicted in Figure 2. The number

of map entries (nodes) is equal to the number of columns in the image matrix. Generalized correlations based on the concept of mutual entropy are used in order to establish significant links in the map.

Both device and clinical data were gathered at patient discharge after CRT implant and at 1-year follow-up. Patient data included gender, age, coronary artery disease (CAD) etiology, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), QRS width, and systolic blood pressure. Adverse clinical occurrences were recorded among the following events occurring within 1-year of follow-up: all-cause mortality, cardiovascular hospitalizations, and deterioration in NYHA functional class.

HR-Co and HR-En indices were correlated with the other HRV-related parameters (HR, SDANN, footprint) by means of single and multiple regressions models. Total variance for the multiple regression model (R^2) was used to assess if HR-Co or HR-En were adequate to explain the HRV phenomenon. An additional multiple regression model, including traditional HRV parameters together with the other available clinical parameters listed above, was built in order to find if the nonlinear indices were additionally correlated with other covariates not associated to autonomic function.

Table 1. Correlation of Complexity and Entropy Indices with Traditional HRV Parameters (HR, SDANN, Footprint Area)

Baseline Data	Univariable Regression		Multiple Regression (HRV) ^a		Multiple Regression (HRV + Clinical Parameter) ^b	
	β	R ²	β	R ²	β	R ²
HR-Co (10.6 ± 4.3)						
HR	60 ± 11	-0.37	0.140	NS		
SDANN	58 ± 27	0.758	0.574	0.396	0.72	0.408
Footprint	31 ± 11	0.790	0.620	0.503		0.492
HR-En (498 ± 335)						
HR	60 ± 11	-0.28	0.079	NS		
SDANN	58 ± 27	0.781	0.610	0.454	0.75	0.404
Footprint	31 ± 11	0.803	0.643	0.514		0.507

Univariable regression, multiple regression with HRV parameters, and multiple regression with HRV + clinical parameters are presented.

^aCovariates: HR, SDANN, Footprint area.

^bCovariates: HR, SDANN, Footprint area, gender, age, NYHA class > II, SBP, QRS, LVEF, CAD.

All correlations significant at $P < 0.01$. HR = heart rate; SDANN = standard deviation of RR intervals; SBP = systolic blood pressure; LVEF = left ventricular ejection fraction; CAD = coronary artery disease.

Baseline values, together with absolute and relative variations for all HRV parameters at 1 year, were presented. In order to examine how both baseline values of nonlinear indices and their variation were associated with adverse clinical outcome, four groups were defined: patients with low/high baseline HRV based on HR-Co values below/above median values, and patients with low/high HRV changes based on HR-Co variation below/above median. Incidence of adverse outcomes together with their confidence intervals was presented in these groups.

In addition, baseline values of clinical and HRV parameters were compared between the two groups of patients with and without adverse clinical events, in order to find significant differences at univariate. A multivariate logistic model with selected variables (those with $P < 0.1$ at univariate or clinically relevant, noncollinear) was used to determine predictors of adverse clinical outcome. To assess the ability of baseline HRV parameters to predict adverse clinical outcome, ROC curves were built both for HR-Co and SDANN: discrimination based on HR-Co was compared to discrimination using the traditional linear parameter by pairwise comparison of the two receiver operating characteristic (ROC) curves.

Finally, a multivariate model was fitted in order to find clinical variables that could predict a positive recovery of autonomic function expressed as HR-Co variation at 1 year.

RESULTS

Sixty patients implanted with a CRT device in seven Italian centers were followed for a median of 12 months. In all patients, baseline and follow-up device data were retrieved and HR-Co and HR-En values were calculated from the footprint image. Correlation of HR-Co and HR-En, separately, with all other HRV and clinical parameters are reported in Table 1. The table shows a relevant correlation of HR-Co and HR-En with SDANN and footprint at univariate, and accounts for an elevated explained variance in the multivariate model including all traditional HRV parameters (HR-Co: $R^2 = 0.72$, $P < 0.01$; HR-En: $R^2 = 0.75$, $P < 0.01$). Furthermore, the inclusion in the model of other clinical covariates, does not add any relevant contribution to the variance (HR-Co: $R^2 = 0.75$, $P < 0.01$; HR-En: $R^2 = 0.80$, $P < 0.05$), meaning that the considered nonlinear indices are strongly linked to autonomic function.

Due to a strongly significant association between HR-Co and HR-En ($\beta = 0.918$; $R^2 = 0.84$; $P < 0.001$), only HR-Co has been used to represent HRV function in the analysis presented for this dataset.

At 1-year follow-up, 9 of 60 (15%) of the enrolled patients experienced an adverse clinical outcome. Baseline clinical characteristics, overall, stratified both for HR-Co, and adverse clinical outcome, as well as their multivariate association to outcome

Table 2. Patient Data Overall and Stratified According to Baseline HR-Co > Median, Baseline HR-Co < Median, and Adverse Clinical Events

	HR-Co <10.5	HR-Co >10.5	P	Events	No Events	P	Hz.r. (95% CI)	P
Male gender (%)	41/60 (68)	19/30 (46)	0.41	6/9 (67)	35/51 (69)	0.91	-	-
Age (m ± SD)	65 ± 10	65 ± 11	0.75	63 ± 13	65 ± 10	0.61	1.02 (0.91-1.10)	-
LVEF (m ± SD)	24 ± 7	25 ± 6	0.44	25 ± 8	24 ± 6	0.95	0.97 (0.36-1.11)	0.71
NYHA Class>II (%)	50/60 (83)	28/30 (93)	0.03	8/9 (89)	42/51 (83)	0.62	1.51 (0.3-0.81)	0.63
SBP (m ± SD)	121 ± 17	122 ± 17	0.99	129 ± 17	120 ± 17	0.17	1.05 (0.97-1.09)	0.09
QRS width (m ± SD)	162 ± 28	159 ± 26	0.36	163 ± 29	156 ± 22	0.50	-	-
CAD (%)	24/60 (40)	14/30 (58)	0.29	3/9 (33)	21/51 (41)	0.65	0.37 (0.05-24)	0.76
Mean HR (m ± SD)	74 ± 11	78 ± 11	<0.005	79 ± 10	73 ± 11	0.21	-	-
HR-SDANN (m ± SD)	57 ± 28	40 ± 13	<0.001	42 ± 19	60 ± 27	0.04	-	-
HR-Footprint (m ± SD)	31 ± 11	23 ± 7	<0.001	23 ± 9	32 ± 11	0.02	-	-
HR-Co (m ± SD)	11 ± 4	-	-	7 ± 3	11 ± 4	0.01	0.71 (0.54-0.95)	<0.02

Univariable and multivariable analysis for the association of variables with of adverse clinical outcome at 1-year follow-up. m = mean; SD = standard deviation; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; HR = heart rate; Co = complexity; En = entropy; Hz.r = hazard ratio, 95% CI = confidence interval.

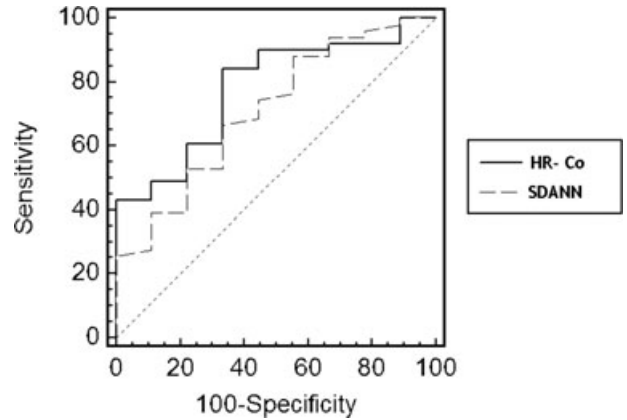


Figure 3. ROC curves for HR-Co and SDANN Vs adverse clinical outcomes.

are presented in Table 2. While only NYHA class > II is associated with a worse autonomic function at baseline, the multivariable model showed that, among all considered covariates, only lower baseline values of HR-Co are associated to adverse clinical outcome in this set of patients implanted with CRT (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.54-0.95; P < 0.02). ROC curves for HR-Co and SDANN (Fig. 3) appear to be similar, showing a good capability to discriminate the clinical outcome under investigation (area under the curve >0.7 in both cases). Difference between the two curves was not statistically significant (area difference = 0.067; 95% CI -0.09; +0.23; P = 0.415).

After the 1-year follow-up, all HRV indices markedly improved. The relative increase were ΔHR: -5.3% (IQR: -11.5/+3.5); ΔSDANN: +61% (IQR: +22/+112); ΔFootprint: +29% (IQR: +7/+83); ΔHR-Co: +60% (IQR: +12/+106), indicating a progressive recovery of HRV with respect to baseline conditions, representative of a generally positive effect of CRT on autonomic function. In a multivariate model to find baseline variables that could predict HRV recovery at 1 year (i.e., increase of HR-Co values above median), none among the available covariates were associated with a significant improvement in HRV except for low baseline values of HR-Co (HR 0.60 95% CI 0.46-0.79 P < 0.01).

When patients were divided according to median values of baseline HR-Co and median increase of HR-Co (Fig. 4), an overall significant difference in incidence adverse outcome was found, with higher incidence of adverse outcome in patients with

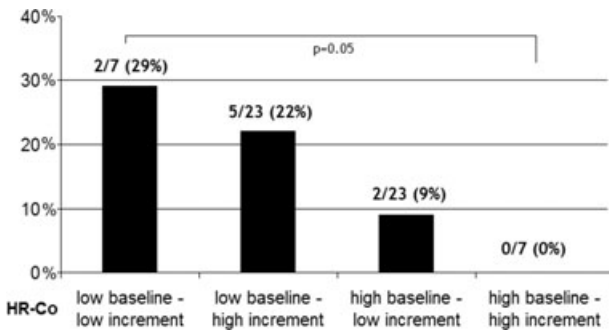


Figure 4. Relative incidence at 1 year of adverse clinical outcomes in group of patients divided according to median values of baseline HR-Co and median increase of HR-Co.

more depressed HRV at baseline and moderate or null recovery during follow-up. Patients with better baseline values of HR-Co and higher improvement during follow-up did not show any adverse outcome.

DISCUSSION

Extensive data on HRV in HF patients implanted with CRT are nowadays retrievable through integrated algorithms of implantable devices. Most of these algorithms are able to process beat-to-beat information through traditional time domain parameters.^{14,15} Recent studies have shown that these parameters carry prognostic information and are linked to the clinical effectiveness of the resynchronization therapy.^{19,21} In addition to traditional parameters of HRV, new indices introduced into device diagnostics, such as the footprint area, have been found to be associated with 1-year mortality.²⁰ The footprint area index is summarized by an image that plots RR intervals versus RR variability (i.e., footprint): this parameter synthesizes the information from several parameters linked to HR and HRV. In this study, we considered a new parameter that could be able to analyze in a different way the underlying structure of the footprint image, with access to a more structured information, the HR-Co and HR-En indices. These measures of image complexity and dispersion hold more information than HR footprint area, because take into account not only the shape, the contour of the image, but also reflects the distribution of local intensity. This means that the HR-Co index may distinguish between images having identical footprint shapes and areas but different distributions inside

the respective contours, with more insights into the RR intervals and related variability.

These data showed that complexity index is strongly associated with HR-related indices traditionally used for autonomic assessment: mean HR, SDANN, and footprint area, both when considered in bivariate or multivariate association. In addition, the high values for variance found in the multivariate model support the hypothesis that a nonlinear index, which represents a more structured information than footprint area, could carry more information on autonomic function than the other traditional indices when considered alone.

Even if results are drawn from a small sample of patients with a limited proportion of events, the analysis of these data showed that the HR-Co index carries relevant prognostic information on outcome of patients implanted with CRT. In particular, HF patients with higher HR-related complexity, representing a less compromised autonomic function, are prone to have better clinical response. On the other hand, baseline HR-Co, being the only parameter correlated to a clinical response in this setting, may be used to identify patients with a poor response, which may require additional interventions and/or better adjustment of the therapy. In this study, a significant increase of HR-related complexity indices and their variation are strongly correlated with the recovery of autonomic parameters and with a positive clinical response to CRT at 1 year. In addition, in accordance to previous publications on different HRV indices,^{18,20} both baseline values and variation over time of the complexity index seem to carry relevant prognostic information, suggesting that repeated or continuous measurements of HRV-related parameters in implantable devices may be a useful tool for risk stratification.

Nevertheless, this study suffer from several limitations: mainly, the small sample size may have affected the statistical significance of any of the associations and, in addition, overfitting of data in multivariate analysis may have occurred due to the limited number of events considered in the follow-up timeframe. At last, observational and noncontrolled nature of the study may have carried additional biases. Therefore, these data have to be considered as preliminary and further studies are necessary to justify complexity as a synthetic index to track HRV in HF patients implanted with CRT.

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