BASELINE HEART RATE-RELATED COMPLEXITY INDEX IN HEART FAILURE PATIENTS PREDICTS CLINICAL RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

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***Abstract — Background*. Studies on the physiology of the cardiovascular system suggested that the generation of the heart rate (HR) signal is governed by nonlinear dynamics. Linear and nonlinear indices of heart rate variability have been shown to predict outcomes in heart failure (HF). *Aim*. To assess if a HR-related complexity index together with other clinical parameters in patients implanted with cardiac resynchronization therapy (CRT) can predict clinical responders at 1 year. *Methods and results*. In 60 patients implanted with CRT (Renewal, Boston Scientific), 24 hour HR data were retrieved at patient discharge and used to compute a Complexity Index (CI) by means of a specific algorithm (OntoSpace™ , Ontonix S.r.l.). In a multivariate model to predict clinical responders to CRT at one year (NYHA class decrease or stable if <III) including age, HR, QRS, ejection fraction (EF), Systolic blood pressure, NYHA class and CI, only CI resulted in a significant prediction of a positive response to CRT (HR: 1.5; 95% CI: 1.1-2; p<0.02). *Conclusion*. HF patients with higher HR-related complexity, representing a less compromised autonomic function, tend to respond better to CRT at one year follow up. Complexity index may be a useful parameter to identify patients who can respond to CRT.**

I. INTRODUCTION

It is known that physiologic systems, both in their healthy and diseased condition, operate under non-stationarity and non-linearity and that non-linear dynamics underlay the generation of most biologic signals [1], [2]. Among these signals, the analysis of heart rate (HR) and its variability (HRV) has become an important and widely used means for assessing cardiovascular autonomic regulation. HRV impairment is associated with many cardiovascular disease states, including ischemic disease [3], [4] and heart failure (HF) [5]-[7], and has been found to be predictor of adverse clinical outcome. Traditional time and frequency parameters as well as methods based on non linear dynamics have demonstrated to provide prognostic information in these 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]. CRT is achieved by implantable devices connected to the heart with endocardial leads; this system is able to pace both ventricles and restore the mechanical sequence of ventricular activation and contraction. Algorithms included in CRT devices, together with increased storage capabilities, allow continuous acquisition of beat-to-beat information on heart rate, enabling additional possibilities for real-time and off-line processing of HRV data [16], [17]. Algorithms associated to CRT devices, essentially based on traditional time-domain analysis, have shown their usefulness in tracking HRV recovery occurring after the implant of CRT devices [18], [19] and in carrying prognostic information on the clinical response to CRT [20], [21]. The value of specific algorithms based on nonlinear indices that process information on CRT devices have not been assessed yet. Recently developed measures of complexity [22] establish an innovative means of characterizing generic dynamical systems. These measures are based on topology (structure of information flow within a system, typically represented via a map) entropy, data resolution (granularity) and coarse-graining (number of state variables chosen to describe the system in question). Objectives of the present study were to assess the predictive value of HR-related complexity and entropy indices with respect to a positive clinical response to CRT and to measure their changes over a follow up of 1 year.

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II. METHODS

Patients which met indications to CRT according to current guidelines were considered eligible for the present study. Current indications to CRT include patients with drug refractory, symptomatic HF of either ischemic or non-ischemic origin with a prolonged QRS complex and a compromised ventricular function (i.e. left ventricular ejection fraction inferior to 35%). A CRT device with defibrillation therapy (Renewal, Boston Scientific) provided with diagnostics on HRV was used to retrieve the necessary data for analysis. The device included the following information, stored on a daily basis: mean, minimum and maximum 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 2-dimensional plot of R-R interval variability versus HR.

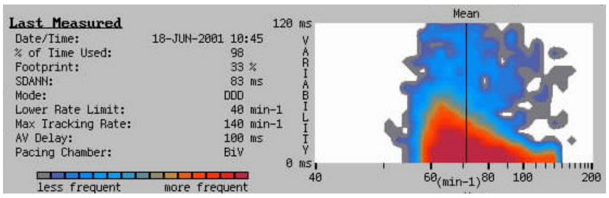

Fig.1. Heart rate-related parameters stored into a CRT device (Renewal, Boston Scientific), including SDANN and footprint.

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 ethyology (CAD), NYHA class, left ventricular ejection fraction (LVEF); QRS width and systolic blood pressure. HR footprint data (data points of the footprint plot) both at baseline and one year follow up were retrieved from device memory and processed with OntoSpace™ (Ontonix S.r.l.) in order to obtain the Complexity (HR-Co) and Entropy (HR-En) indices.

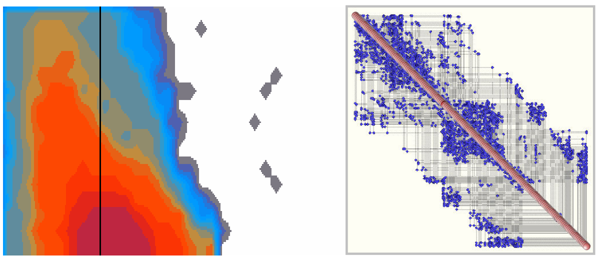

Fig.2. HRV image (left) with the corresponding Process Map, reflecting the structure of local correlations within the image.

The process of computation of image complexity is as follows. The image is transformed into an N x M pixel map, whereby each pixel is an integer ranging from 1 to 16. The resulting N x M matrix is treated as an equivalent system of N state variables sampled at M equidistant intervals. A proprietary entropy-based image-processing technique implemented in OntoSpace™, establishes the existence of local structures within the data matrix, producing the so-called Process Map (fig. 2). The Process Map is

TABLE I
PATIENT BASELINE DATA

male gender (%)	68
Age; (m±SD)	65±10
NYHA Class (II/III/IV)	10/46/4
CAD (%)	40
LVEF (m±SD)	24±7
SBP (m±SD)	121±17
QRS width (m±SD)	162±28
Mean HR (m±SD)	74±11
HR- SDANN (m±SD)	57±28
HR- Footprint (m±SD)	31±11
HR-Co (I; med; III)	7.1; 10.5; 13.4
HR-En(I; med; III)	219; 427; 694

m: mean; SD; sdtandard deviation; med: :median; I: 25th percentile; III: 75th percentile; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; HR: heart rate; Co: complexity; En:entropy

characterised by N nodes, aligned along the diagonal. Dependencies between the N state variables are indicated via connectors located off the diagonal. The distribution pattern of the connectors depends on the pixel size (N and M) and on the overall properties of the image. The topological properties of the Process Map are used to determine the map complexity which is equated to the image complexity. The HR-Co index may be regarded as a measure of the amount of "structured information" in the footprint image itself. This measure of image complexity holds more information than HR footprint area in that it not only takes into account the shape of the contour of the image but it also reflects the distribution of local colour intensity. This means that the HR-Co index may distinguish between images having identical footprint but radically different colour distributions within the respective contours.

Percentage variations of HR-Co and HR-En between patient discharge and one year were calculated and fitted into a multiple regression model to analyze their correlation with variations of other clinical and HR parameters. A positive response to CRT was defined considering one year data; an increase in LVEF of at least 15% or a 15% decrease in end-systolic volume identified instrumental responders, while improvement in NYHA functional class (or stable if II at baseline) identified clinical responders. Baseline values of clinical, HR and complexity parameters were compared between the two groups of responders and non responders, in order to find significant differences at univariate. A multivariate logistic model with selected variables (those with $p<0.1$ at univariate, non collinear) was used to determine predictors of a positive response to CRT.

III. RESULTS

Sixty patients were followed up for a median of 12 months. Baseline clinical characteristics, device stored HRV data, and complexity data are represented in Table I.

At one year follow up, 51/60 patients showed clinical improvement as assessed through NYHA class, while 31/60 patient were instrumental responders.

Complexity indices markedly increased 1 year after CRT implant: ΔHR-C +60%[12-106]; ΔHR-E +102%[10-239], indicating a progressive recovery of HRV with respect to baseline condition. The multivariate regression model showed that complexity indices variations accounted for a significant explained variance (HR-C: R^2=70.15%, $p<0.001$; HR-E: R^2=67.1%, $p<0.001$). Footprint area(HR-C: β=+0.54, $p<0.001$; HR-E: β=+0.58, $p<0.001$) and SDANN (HR-C: β=+0.25, $p<0.05$; HR-E: β=+0.24, $p<0.05$), accounted for the major contribute, while all the other parameters were weakly or non significantly correlated. In the model built to predict clinical responders to CRT at one year (NYHA class decrease or stable if <III) age, HR, QRS, ejection fraction (EF), Systolic blood pressure, NYHA class and HR-Co were included. Only HR-Co resulted in a significant prediction of a positive response to CRT (HR: 1.5; 95% CI: 1.1-2; $p<0.02$). None of the parameters showed significant differences for prediction of instrumental responders.

IV. Conclusion

Extensive data on HRV in HF patients implanted with CRT can nowadays be retrieved though algorithms integrated in 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]. This study demonstrated, through off-line analysis of HR data retrieved from implantable devices, that complexity carries relevant prognostic information on device therapy effectiveness. In particular, complexity may be a useful parameter to identify patients who can respond to CRT: HF patients with higher HR-related complexity, representing a less compromised autonomic function, tend to respond better to CRT. CRT also is associated at one year with a significant increase of heart rate related complexity indices and their variation is strongly correlated with the recovery of autonomic parameters. Further studies are necessary to justify complexity as a synthetic index to track status of HF patients implanted with CRT.

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