Signaling prodromes of sudden cardiac death

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Abstract

The new criteria in detection of ARVC/D produced more subtle noninvasive parameters that raised sensitivity in diagnosis. Since heart rate dynamics have prognostic significance for the progression of a disease and for mortality, the main objective was to explore its value in disclosing risk for serious arrhythmias.

Out of 100 ARVC/D patients, 35 with normal ECG Holter recordings (PVC<100) and no medical treatment (either antiarrhythmic or proarrhythmic drugs) were analyzed according to severity of ARVC/D (Group 1/mild, n=23 and Group 2/overt, n=12) and regarding positive late potentials (noise interval between 0.1-0.3 μV). Severity of ARVC/D is defined: group 1 with no clinical recognizable signs and group 2 with clinical readily recognizable signs. Group 3 (control) consisted of 35 randomly assigned healthy subjects. The differences between the 3 groups were assessed by ANOVA followed by Bonferroni`s post hoc multiple-range tests.

NLD methods, as opposed to linear time and frequency, show very significant differences between investigated groups vs. control. NLD methods by mean of the standard deviations of all NN intervals of sinus beats for all 5-minute segments (SDNN index) showed prevalence of parasympathetic activity as opposed to control. This was even more obvious through interpolation of data as % of deviation of Mean NN interval in function % frequency (p<0.005).

NLD methods describe complex rhythm fluctuations in ARVC/D patients that put insight at proarrhythmic potential of affected subjects. Furthermore, in combination with late potentials they improve recognizing hidden risks for serious arrhythmias.

KEY WORDS: sudden cardiac death, arrhythmogenic right ventricular dysplasia, heart rate variability, non linear dynamics.

INTRODUCTION

The variation of heart rate over time within the period between consecutive heartbeats, also known as heart rate variability (HRV) [1] , is in a close connection to external environments stimuli. The heart rate variability describes the fluctuations in the interval between consecutive heart beats (RR interval) [2,3], by analysing two different periods through 24 hours active and resting (day and night). Autonomic nervous system (ANS) plays an important role in the regulation of physiological processes of the human organism. It is a measure that can be used to assess the ANS modulation under physiological and pathophysiological conditions [4,5,6,7,8,9]. Among the techniques used in its evaluation, the heart rate variability (HRV) has emerged as a simple and non-invasive measure of the autonomic impulses, representing one of the most promising quantitative markers of the autonomic balance [10]. HRV analysis is very complex for interpretation, especially recently with the increasing number of mathematical testing models described in literature, but it opens newly horizons for clinicians. NLD methods are therefore valuable tool to investigate the amount of HR fluctuations around the mean HR and can be used as a mirror of cardio respiratory control system [11]. Partial information on these phenomena can be derived from time-dependent spectral analysis of HRV using the wavelet transform as such was found to be valuable in detecting interventricular conduction abnormalities [12]. Cardiovascular screening in young athletes in one targeted study has achieved sufficient result to prove necessity for establishing strategy for national sports databases [13]. *A priori* hypothesis was made that baroreceptor stimuli were depleted in ARVD/C affected hearts in comparison to healthy hearts and that such behavior, if detectable, should be acknowledged. The main aim of the study was to see if non linear dynamic methods could be useful in predicting risk of sustained VT or do nonlinear time series analysis methods have prognostic value.

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MATERIALS AND METHODS

Subjects

The Serbian database of ARVC/D patients established in 1998. by Dr Ivana Vranic served as a pool of positively diagnosed patients which comprised 100 non relatives. The diagnosis was made upon the score system criteria made by McKenna in 1994 (that comply with the newest Marcus 2010). From the above described population, only those who had had clinically normal ECG Holter recordings (only 100 premature ventricular couplets (PVC) of LBBB pattern) and no medical treatment (n=35) were subject to analysis of HRV, having in mind that incidence of ARVC/D in general population is around 1/1000. Further division of these patients was made in two separate subgroups according to the presence of late potentials (SAECG) with noise interval between 0.1-0.3 μV. Signal averaged ECG with: HQRS<120ms, LAHF>20 and RMS<40 were considered negative and vice versa. Group 1 (n=23) mild form had RV enlargement<3cm, epsilon wave defined as prolongation of QRS complexes in leads V1-V3 as compared to V4-V6 (ratio of the sum of the QRSd in leads V1–V3 versus V4 – V6 of ≥ 1.2) and localized aneyrisms seen on radionuclide ventriculography of RV in the region of proximal part of interventricular septum. This group was compared to Group 2 (n=12) overt form of ARVC/D who had RV enlargement<3.5cm, epsilon wave defined as V1-V3/V4-V6>1.1 and localized aneyrisms seen on radionuclide ventriculography of RV in the region known as triangle of dysplasia. Both groups of selected patients were further divided based on late potentials as A) positive (N=22), and B) negative (N=13). Subjects with severe form of ARVC/D were excluded, since they had many occurrences of arrhythmic events, which would alter HRV measures. Group 3 (n=35) consisted of randomly assigned healthy controls (out of 45) selected from our medical staff (age 34.80 ± 4.21and gender M17/W18). All the study individuals were asked to maintain habitual activities and their normal asleep-awake rhythm during the recording session, they all gave informed consent at the protocol which was approved by Institutional review committee of the Medical School of Belgrade. Control Holter 24 hour monitoring with conventional measures of time and frequency domain together with parameters from symbolic dynamics was performed in 12 ± 6 months. Any form of VT recorded on later was regarded as positive risk, because they generated transient increases in sympathetic tone and were considered main factors of potentially triggering fatal arrhythmias.

Heart Rate Variability

Three-channel 24-hour Holter ECG monitoring was performed in all subjects using Schiller model microvit MT-101 recorder. The device has 12-bit amplitude resolution with 1000 Hz sampling frequency. Holter recordings were subsequently analyzed by Schiller medilog® AR4 software. The following time domain parameters of NN variability were obtained: NN [%], MeanNN [ms], SDNN [ms], SDANN [ms], SDNNidx [ms], dNN tachogram, rMSSD [ms], NN50, pNN 50 [%], NN100, pNN 100 [%], NN200, pNN 200 [%]. Frequency domain parameters of LF, HF and LF/HF ratio were also calculated.

Statistical Analysis

Discrete data are presented as frequencies and percentages, and continuous variables as means and standard deviations or as medians and interquartile ranges if the distributions were skewed (Table 1). Fisher exact test was used for comparison of proportions of late potentials between groups (Table 2). The differences between the 3 groups were assessed by ANOVA followed by Bonferroni`s post hoc multiple-range tests. Student`s paired T test was used to assess differences in clinical variables between ARVC/D patients with positive and negative LP. Normal values for HRV parameters in healthy controls were used to determine sensitivity, specificity, predictive values, and accuracy to assess reliability of HRV as diagnostic and prognostic methods. All analysis were done using IBM SPSS software version 19.

TABLE 1. Clinical characteristics of 35 study patients as opposed to controls

	Group 1	Group 2	Group 3
Number of subjects	23	12	35
Age (years)	33.93±6.27	38.29±6.05	34.80±4.21
Gender (men/women)	11/12	5/7	17/18
BSA (m^2)	1.63±0.09	1.55±0.07	2.37±0.23
BMI (kg/m^2)	23.76±3.24	21.86±5.33	22.07±1.25
Serum Potassium concentration (mmol/L)	3.98±0.19	4.17±0.18	4.07±0.29
Family history of sudden death (%)	36	29	0
Asymptomatic patients (%)	36	43	100
Palpitations positive symptom (%)	7	14	20
Syncopy positive patients (%)	0	14	0
Atipical chest pain (%)	36	14	0
Clinically impaired RV (%)	0	0	0
Dyspnoic patients (NYHA>I) (%)	7	14	0
Hypertensive patients (%)	0	0	0
Hypotensive patients (%)	0	0	0
ECG positive arrhythmia LBBB (%)	0	29	0
Epsylon wave on ECG positive (%)	7	29	0
Positive SAECG potentials (%)	36	29	0
Enlargement of RV (%)	14	57	0
Localized aneyrisms of RV (%)	7	43	0
EF RV (%)	34	33	55
EF LV (%)	60	58	55
TAPSE	13.56±2.66	13.76±2.74	28.23±2.73

RESULTS

The baseline clinical characteristics of the study population are summarized in Table 1. Age did not significantly differ between the 3 study groups. There was no significant difference in regard to arrhythmia presence on the Holter recordings (in total no more than 100 monofocal PVC and no other form of arrhythmia) among the observed 3 groups. Presences of LP have not differed among investigated groups, Table 2. Summary data on NN means and time domain measures, comparing ARVC/D patients with control subjects, are presented in Table 3. rMSSD was higher in group 1 vs. group 3 and on the contrary, pNN50[%] was lower in group 1 vs. group 3. This is possible, even though these two values usually have a high mutual correlation with each other, because there is a high difference in HRV between these two groups. During a mean follow up of 12 ± 6 months, no deaths occurred, but 8 pts (22%) experienced arrhythmic events on control Holter regarded VT. No other HRV measure except symbolic dynamics achieved statistical significance in prognosis of fatal arrhythmias in the multivariable analysis Table 4. In the patients who experienced arrhythmic events in the follow-up Holter, NLD results were predictable of VT within the same group ($p<0.05$) Table 4. The 24-hour NN tachogram showed peaks of turbulence onset and rebound effect of slowing down in both groups 1 and 2, which was found to be statistically significantly different as compared to controls ($p<0.005$). Proportion of adjacent NN intervals that differed more than 50ms showed a very significant difference between all 3 groups ($p<0.005$), while it showed no difference inside the same group in comparison to LP. Time domain measures of NN variability were significantly higher (subgroup B) while asleep than while awake in ARVC/D patients who had negative late potentials, and were significantly lower in those with positive LP (subgroup A) $p<0.05$ (data not showed). Importantly, pNN50(%) showed significant differ-

TABLE 2. The distribution of SAECG is the same across categories of Group, *p* value>0.05

	A: SAECG positive	B: SAECG negative	TOTAL
Group 1	15	8	23
Group 2	7	5	12
TOTAL N pts	22	13	35

SAECG: late potentials

TABLE 3. Time domain average NN variability in ARVC/D patients (Group1, 2) and in Control Subjects (Group 3)

	Group 1	Group 2	Group 3
Mean 24 hour NN	807±63	844±72	756±29
24 hour SDNN	140±52	180±39	98±12
24 hour SDANN	120±46	165±35	83±13
24 hour SDNN idx	31±28*	62±8	53±26
24 hour rMSSD	37±22*	40±13*	27±13
24 hour pNN50(%)	1.3±0.9‡	13±7‡	6.1±2.3

* ($p<0.05$) , ‡($p<0.005$)

TABLE 4. Time domain average NN variability in ARVC/D patients (Group1, 2) and in Control Subjects (Group 3)

	Group 1	Group 2	Group 3
LF (ms)	17± 8 *	31± 13 ‡	13.6 ± 1.3
HF (ms)	8.2 ± 5 *	23 ± 12 ‡	5.4 ± 4.0
LF/HF	1.89 ± 0.1 *	1.34 ± 0.4 *	2.4 ± 1.8
Sym Dyn EN	4.07 ± 0.32	3.78 ± 0.69	3.24 ± 0.49
Sym Dyn FW	48.9 ± 17.5 ‡	43.7 ± 17.5 ‡	63.4 ± 7.9

* ($p<0.05$) , ‡($p<0.005$)

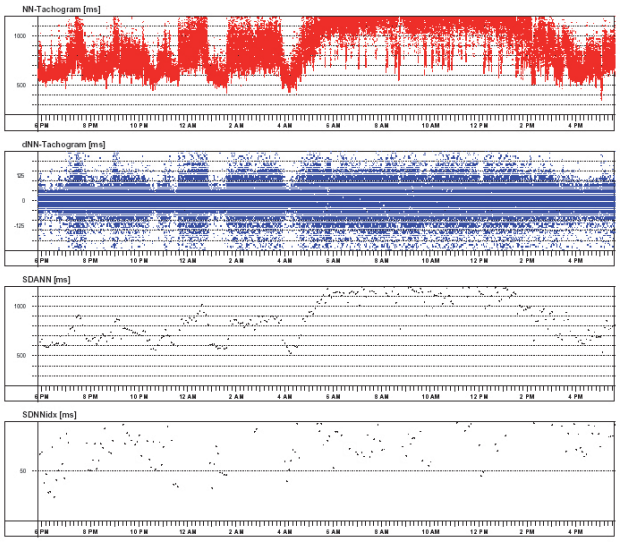

FIGURE 1A. dNN Tachogram (ms) as symbolic dynamics, vs. SDNNidx (ms) as renormalized entropy in ARVC/D pt

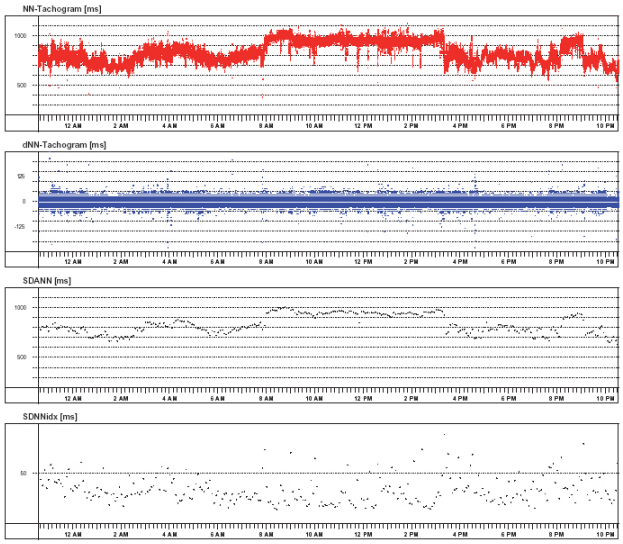

FIGURE 1B. dNN Tachogram (ms) as symbolic dynamics, vs. SDNNidx (ms) as renormalized entropy in healthy control

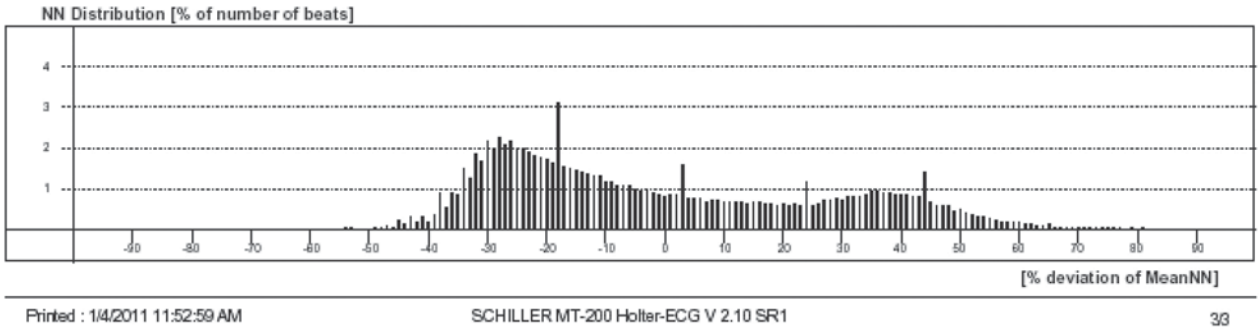

FIGURE 2A. ARVC/D patient-NLD information from time domain parameters

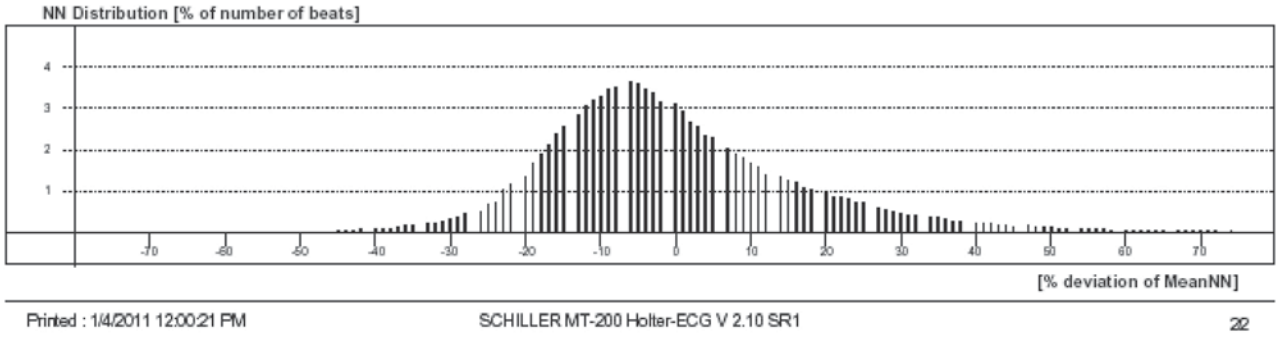

FIGURE 2A. Healthy control- Gaussian distribution NLD from time domain parameters

ence between two groups (1 and 2) and the control group, table 3 (p<0.005), which represents strong diversity of electrical currents distribution in ARVC/D patients. rMSSD, however, showed difference between ARVC/D patients and the control group (p<0.005), whereas group 1 and group 2 were not significantly different in those parameters (p>0.05). This was particularly obvious during interpolation of gathered data displayed on Figure 1 (A/B) regarding SDANN and SDNNidx. Mean of the standard deviations of all NN intervals of sinus beats for all 5-minute segments (SDNN index) showed prevalence of parasympathetic activity as opposed to control (Figure 1(A/B)). This was also graphically shown on Figure 2(A/B), by interpolating data as deviation percentages from mean NN interval in function of frequency (p<0.005).

DISCUSSION

It is well known that sympathetic stimulation causes an increase in heart rate (HR) through the firing rate of pacemaker cells in the heart`s sino-atrial node [14]. Parasympathetic activity, primarily resulting from the function of internal organs (i.e. heart) decreases the firing rate of pacemaker cells and the heart rate, thus providing a homeostatic balance. The opposite rhythmic contributions by two components of ANS modulate the heart rate (NN) intervals of the QRS complex in the electrocardiogram at certain frequencies. Contrary to parasympathetic activity associated with the higher frequency range (0.15-0.4Hz), sympathetic activity is associated with the low frequency range (0.04-0.15Hz) [14]. Even though HRV does not represent sole modulation of the heart by the ANS it represents the quality of contacts between baroreceptors and efferent nerves that modulate response of low potentials [14,15]. Also, if such pattern should exist in ARVC/D it could be readily detectable and/or worthy in the follow up, concerning progressive nature of ARVC/D disease and its various clinical forms. It is important though to accomplish that the control of the cardiovascular system is maintained only in part by the autonomic nervous system (ANS), by its afferent and efferent nerves to the heart. On the other hand, ANS influence is rather dependant on body physiological and pathological conditions, and its influence on the heart is pendulous to information from baroreceptors, chemoreceptors, atrial receptors, ventricular receptors, among others. Due to the unstable membrane potential of the myocites located in the region of sinoatrial node, corresponding action potentials are derived periodically at a fairly constant level of rhythmical heart beats. This relatively constant frequency generated by the autorhythmicity of the sinoatrial node is modulated by many factors that add variability to the heart rate signal at different frequencies. However, it is well established that the control of the denervated heart is performed based on the venous return, atrial receptor stimulation, atrial stretch and hormones and other substances in the circulatory system [16,17]. Among them ultra-low frequencies

(ULF>5-h cycle length) dictate the circadial rhythm, which strongly corresponds to sympathetic nerve discharges [18]. On the other hand, the symbolic dynamics is with the closest connection to physiological phenomena with respect to external *milieu* conditions [19]. By means of this method, the inner motions of the time series can be investigated, since they are easy to interpret. Standard parameters of time domain often leave these dynamics out of consideration. The renormalized entropy, as a measure of relative degree of order, is a further suitable method for the detection of patients at risk for SCD. Changes in the HRV patterns provide a sensible and advanced indicator of health involvements, so one is to find stationary periods (i.e. during the night) in the time series, being aware that instationarities can sometime mislead the track. Still, instationarities vary among ARVC/D patients which points to a higher risk. Whereas higher HRV signals good adaptation and characterizes a healthy person with efficient autonomic mechanisms, impending lower HRV is frequently an indicator of abnormal and insufficient adaptation of the autonomic nervous system, provoking poor patient's physiological function. These instationarities are less different during active period of the day in ARVC/D patients, and more different during the resting period as compared to controls. This study applies new methods of non linear dynamics and compares these with conventional methods of heart rate variability and high resolution ECG analysis in order to improve the reliability of high risk stratification. Noteworthy, the patients with the more severe RV enlargement would be expected to be at higher risk, but NLD has failed to detect any significant difference between group 1 and group 2, Table 4. This is because of the existing opposite effect produced by baroreceptor discordance induced by pressure stimulation and subsequent delay of reflexive connection due to interspersed apoptotic process. Moreover, analysis of active/resting period give evidence of risk stratification in alike manner over and above other criteria that are listed in many articles on risk stratifications in ARVC/D as well as other criteria to identify risk in the individual patient such as RV enlargement, presence of epsilon wave or localized aneyrisms per se or in combination. NLD adds to risk assessment in ARVC/D because it had showed strong correlation with future arrhythmic events of sustained VT. Applying symbolic dynamic methods to 24 h Holter ECG, obtained results advocate higher dynamics in resting period in both groups of ARVC/D patients, as opposed to the control group, Table 4. Also, presented results show that ARVC/D patients have specific loss of HRV control most probably due to subsequent discord of autonomic neural regulatory mechanism dependant on the contact between cardiomiocite *an groux* mass of right chamber and HR. That is especially obvious regarding absence of circadian variations of time domain that carries prognostic implications *per se* [20,21,22,23]. Despite of the fact that HRV is altered in diseased hearts of any etiology, patients with ARVC/D have common ground of different baroreceptor signal information coming from the right heart to ANS. Noteworthy, it should be emphasized that pathogenesis of ARVC/D is pretty complex and driven by several factors. One of them is intrinsic delay in propagation of the electrical impulse through the heart and septum. Due to the phenomenon of interventricular dependence, baroreceptor signal system of RV gives an array of information which is not constant. Nevertheless, subsequent predominance in influence that respirative pressure changes undertake upon diminished number of heart baroreceptors that are interspersed on fibro-fatty RV is the other crucial mechanism. Even more, such vulnerable nonharmonious balance could easily be disrupted by physical exertion (due to adrenergic influence). This imposes disbalance in information that ANS receives from both sides of the heart (LV usually spared). The methods of NLD describe complex rhythm fluctuations in ARVC/D patients that put insight at proarrhythmic potential of affected subjects (Figure 1A/B). Furthermore, in combination with late potentials they improve recognizing hidden risks for serious arrhythmias. This leads to an improved discrimination between a normal (healthy persons) and an abnormal (high risk patients) type of heart beat generation. Some patients with an unknown risk exhibit similar patterns to high risk patients and this suggests a hidden high risk (Figure 2A/B).

This study indicates probable explanation why SCD prone patients feel good during sport activities, and faint with fatal arrhythmias only after ceasing them [24,25,26,27]. Possibility for this occurs very early, even at the clinically silent stage of ARVC/D, where methods of NLD can find their way through. However, due to the small number of subjects, these results need to be confirmed by a larger and especially prospective clinical investigation.

CONCLUSION

This is a primary clinical study in ARVC/D patients with methods of non linear dynamics in HRV analysis which move frontiers in the field of prevention of SCD. The basic results show positive outcome that seem to confirm stated hypothesis. Although time domain methods enable the quantification of HRV on different time scales, NLD methods enable clear distinction between those who carry hidden risk for SCD. Finally, they show the advantages of combining all HRV methods with late potential analysis in improving the precision of high risk stratification.

DECLERATION OF INTEREST

There is no conflict of interest to declare.

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