A Biexponential Approach for Assessing Parasympathetic Reactivation after Submaximal Exercise

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Abstract

The occurrence of cardiac events and sudden death in Brugada syndrome (BrS) patients during sleep or rest, suggests that the parasympathetic activity of autonomic control might play a key role in this disease. In this study, the instantaneous heart rate during an exercise test was assessed in 115 BrS patients, of whom 25 were symptomatic. The recovery period lasted 6 minutes and included two phases of 3 minutes each called active and passive recovery. A bi-exponential function was used to model the shape of heart rate decay during recovery, from which the heart rate recovery (HRR) index was determined throughout the entire period. The time-course of HRR was investigated and compared by separating patients according to symptoms, sex and SNC5a mutation. Results showed that asymptomatic patients presented larger HRR values than the symptomatic group for most of the time. The temporal evolution of the p-value revealed that significant differences between these groups begin to appear after 2.5 minutes of recovery lasting about 0.5 minutes. The critical time instant was found at minute 2.85, being HRR= 46.0±10.9 beats/min (asymptomatic) and 41.6±9.7 beats/min (symptomatic), p=0.031. Regarding sex, relevant differences appeared from minute 1.5 to minute 1.7, with the critical timing found at minute 1.62 (p=0.043, HRR=0.9±8.2 beats/min for women and 33.9±9.5 beats/min for men). We concluded that assessing the HRR beyond classical intervals (1 or 2 min) might help to determine which asymptomatic patients are most at risk for developing future adverse cardiac events.

1. Introduction

Brugada syndrome (BrS) is a genetic pathology associated with a high risk for sudden cardiac death (SCD) occurring mostly during the sleep or resting, in patients with an apparently normal structural heart. The presence of a coved type-1 ECG pattern in ≥ 1 precordial lead placed in the 2nd/3rd intercostal space, is the only type that can had a BrS major diagnostic marker. [1].

One of the biggest challenge in BrS is related to patient risk stratification and the definition of the best treatment approach. The placement of an implantable-cardioverter defibrillator (ICD) is the only recommended treatment for symptomatic patients. However, in the asymptomatic patients this decision is more complex, while they represent between 60% of the BrS population.

Most cardiac events in BrS patients occur when they are at rest or during sleep, indicating that the autonomic control, and in particular the vagal activity, might plays a key role in triggering cardiac arrhythmias. When evaluating the functioning of autonomic control through representative characteristics in some specific scenarios, quantitative markers capable of separating between symptomatic and asymptomatic patients could be found, and even more, to assist in the decision-making process for the implantation of an ICD in the symptomless group.

The heart rate recovery (HRR), defined as the decay in heart rate after the exercise peak when lasting typically 1 or 2 minutes of recovery, has been investigated in many studies proving to be a good predictor of all-cause of mortality and of cardiovascular death. The period in which the HRR is evaluated results from a combination of the parasympathetic/vagal reactivation and sympathetic withdrawal, clearly reproduced by the recovery period of an exercise test. In the case of BrS, this marker has been related to the presence of increased ST segment elevation after sub-maximal effort, being higher for those patients who developed future cardiac events[2], but not specifically with the presence of symptoms.

In this work, we aimed at further characterizing the parasympathetic response in BrS patients by continuously assessing the HRR throughout the complete recovery period of an exercise test. Afterwards, we searched for potential time intervals in which there were significant differences between patient groups according to sex, SNC5a mutation and more importantly, between symptomatic and asymptomatic patients.

 ISSN: 2325-887X DOI:10.22489/CinC.2017.306-390

Group	Symptomatic n=25	Asymptomatic n=80	Total n=115
Sex (males)	19 (63%)	44 (86%)	63 (78%)
Age (years)	42.0 ± 16.3	44.8 ± 9.9	43.7 ± 7.1
Symptoms:	7 (23%)	13 (25%)	20 (25%)
- *Cardiac arrest*	3 (10%)	7 (14%)	20 (25%)
- *Syncope*	4 (13%)	6 (12%)	10 (12%)
- *Palpitation*	-	1 (2%)	1 (1%)
- *Near syncope*	1 (3%)	-	1 (1%)
Spontaneous Type-1 ECG	12 (37%)	16 (31%)	28 (35%)
ICD implanted	12 (40%)	23 (45%)	35 (43%)

Table 1. Main clinical features of the study population

2. Materials and methods

2.1. Population

The study population comprises 110 (85 men) patients suffering from BrS enrolled in a multicenter french study. 25 patients had previous clinical symptoms (the symptomatic group) including syncope, PTV/VF or SCD, which were implanted with an ICD. The remaining 85 patients (the asymptomatic group) did not presented any clinical BrS-related symptoms at the moment of the diagnosis. In the Table 1 are shown the main clinical parameters related to this population [3].

2.1.1. Test protocol

• *Exercise phase*: An initial warming-up phase of 2 minutes by pedaling at 50 W (30 W for women), followed by consecutive 2-minute periods with increments of 30 W (20 W for women) each until reaching at least 80% of the maximal theoretical heart rate, $HR_{max} = 220 - age$.
• *Recovery phase*: 3 minutes of pedaling with the initial workload of 50 W followed by 3 minutes of passive recovery at rest.

2.2. Preprocessing

All ECG signals were preprocessed as follows: 1) automatic QRS complexes detection and subsequent visual inspection, 2) baseline drift attenuation via cubic spline interpolation, 3) 4-th order Butterworth low pass filtering at 45 Hz to remove muscular noise and 4) wave delineation using an evolutionary optimization approach [4].

2.3. Extraction of the heart rate series

After QRS complexes detection, the RR series were subsequently generated for each patient using the equation below.

$$RR[i] = R[i] - R[i-1], i = 1, 2, ...N \quad (1)$$

where i is the number of the actual beat and $R[i]$ its position in time. These series were computed during the entire duration of the recordings, including both the exercise and the complete recovery (six minutes) periods.

2.4. HRR curve and HRR marker

To evaluate the HRR marker, we referred to the maximum peak exercise as the physiologic start of recovery, as stated by Freeman et al. in [5]. For modeling the HRR curve, we used two different options. The first one was a exponential of the general form, typically used in many HRR-related studies to characterize the shape of the recovery process.

$$C_{\text{HRR}}(t) = HR_{\text{Rest}} + (HR_{\text{Peak}} - HR_{\text{Rest}})e^{(kt)} \quad (2)$$

where HR_{Rest} is the mean HR at baseline, k is the decay coefficient that control the rate of the curve decay, and t is the time lapsed from the peak HR in minutes. The second option evaluates a bi-exponential decay model of the form:

$$C'_{\text{HRR}}(t) = Ae^{(-\tau_1 t)} + Be^{(-\tau_2 t)} \quad (3)$$

where τ_1 and τ_2 can be seen as the decay rates of two exponential processes, one fast and one slow, that are mostly represented during the active and passive periods of the recovery phase, respectively. Likewise, the parameters A and B account for the amplitude change in HR decay caused by the two exponential processes controlled by τ_1 and τ_2.

Before fitting the function to HR values, all the HR series were resampled at 4 Hz because the original series were not uniformly sampled.

Once the HRR curve is fitted throughout the recovery, the difference between its first value $C_{\text{HRR}}(t_0)$ (corresponding to maximum HR) and those values of the curve

evaluated at every second, $C_{\text{HRR}}(t)$, was calculated until the end of the recordings to obtain the final HRR series, expressed as $\text{HRR}(t) = C_{\text{HRR}}(t_0) - C_{\text{HRR}}(t)$. Figure 1 shows an example of the HR evolution for a particular patient and the resulting HRR curve.

2.5. Statistical analysis

The model that best described the heart rate recovery process was selected according to the RMSE values of the fitting, calculated and averaged for the whole population. The coefficients obtained from the fitting step using the selected final model were compared among different pairs of patient groups. The same analysis was performed to the HRR values evaluated along the whole recovery. Results were presented as mean $\pm$ SD. Patient groups differences were evaluated by using the Wilcoxon's rank-sum test, setting the level of significance at 0.05.

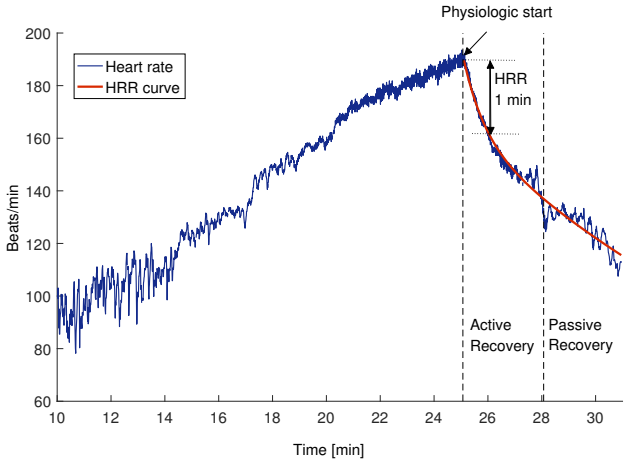

Figure 1. Example of HRR curve fitted on a real stress test recording

The most important comparison regarding the study population was the one involving patient groups selected according to symptomatology (symptomatic and asymptomatic groups). Secondary analysis were also performed by grouping patients according to sex and genetic screening results (SCN5A mutation).

Finally, the discriminative power of the relevant results was evaluated, generating the associated ROCs curves and obtaining the corresponding AUC values.

3. Results

Figure 2-a illustrates the time-course of HRR for the population, clustered and averaged according to symptomatology every 10 s during the whole recovery period. From the figure it can be observed that, for all the presented intervals, HRR was larger in asymptomatic patients as compared to symptomatic patients. Moreover, p-values obtained from the statistical test (see Fig. 2-b) applied on each interval, showed that differences between groups start to be significant after 2.5 minutes of recovery, and lasting during the next 0.5 minutes. The p-value's time course also indicates that the most relevant difference among groups occurred at minute 2.85 ($p = 0.031$) of the recovery, with HRR = 46.0 ± 10.9 and 41.6 ± 9.7 beats/min for both the asymptomatic and symptomatic groups, respectively. Then, after the third minute, significant differences begin to disappear gradually until the end of the recovery.

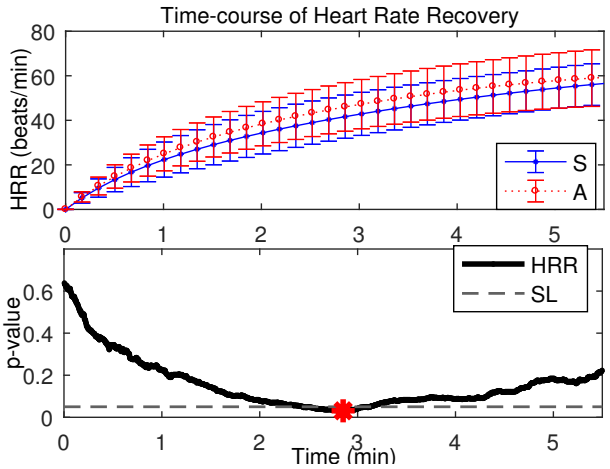

Figure 2. a) Time-course of the heart rate recovery along the recovery period of the stress test for the two Brugada subgroups. b) Time-course of the p-values obtained when applying the statistical test on the two subgroups

The comparisons taking into account the sex of the patients and the presence or absence of the mutation are presented in Fig. 3. The difference between these two analyses and the one presented in Fig. 2 are clearly observed when looking at the p-value time-course. In the case of sex, the differences began to be slightly significant from the minute 1.5 till the minute 1.7, having the minimum p-value at minute 1.62 ($p = 0.043$), with 30.9 ± 8.2 beats/min for women and 33.9 ± 9.5 beats/min for men, as observed in Fig. 3-a and 3-c. In the case of the SCN5A mutation, no significant differences were found throughout the recovery period.

Regarding the HRR curve's coefficients (A, B, τ_1 and τ_2), non-significant differences were found to be in any of the three different groups comparison, as can be inferred from the shape of the average HRR curve obtained for each group.

The ROC curves associated with the discriminative power of HRR when distinguishing between symptomatic

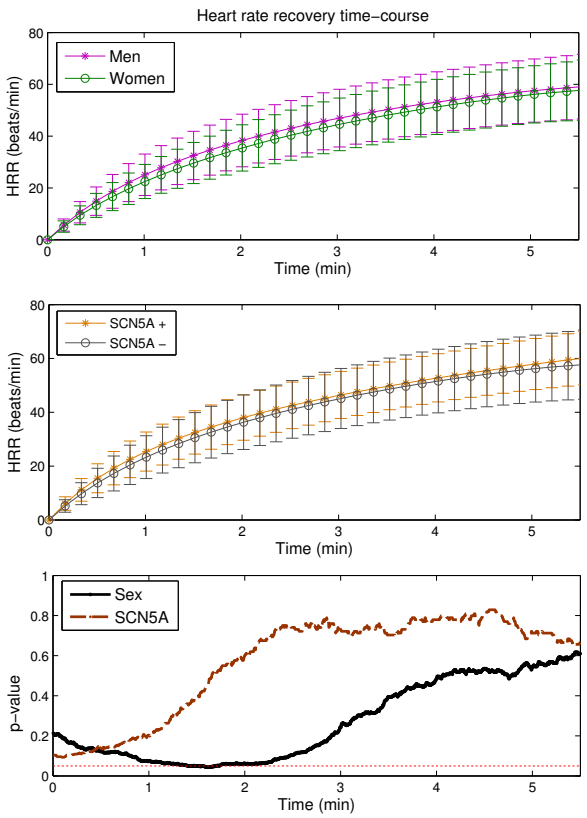

Figure 3. a) and b) Time-course of the heart rate recovery along the recovery period for the population grouped by sex and SNC5a mutation, respectively. c) Time-course of the p-values obtained when applying the statistical test to the involved subgroups

and asymptomatic patients is displayed in Fig. 4 for the interval with the critical difference between groups according to results showed in Fig. 2.

4. Discussion and conclusions

This study has shown that assessing the heart rate recovery beyond classical intervals traditionally used for this purpose (1 or 2 min after the exercise peak), could be useful in identifying symptomatic or asymptomatic patients in a population with Brugada syndrome. In the case of asymptomatic patients, where the decision of implanting an ICD is usually complex, this kind of analysis may help to select in conjunction with other electrophysiological markers, those patients with high risk of suffering adverse cardiac events in the future.

Acknowledgements

D.R. acknowledges the financial support of the Fondation Lefoulon-Delalande, Institut de France, France.

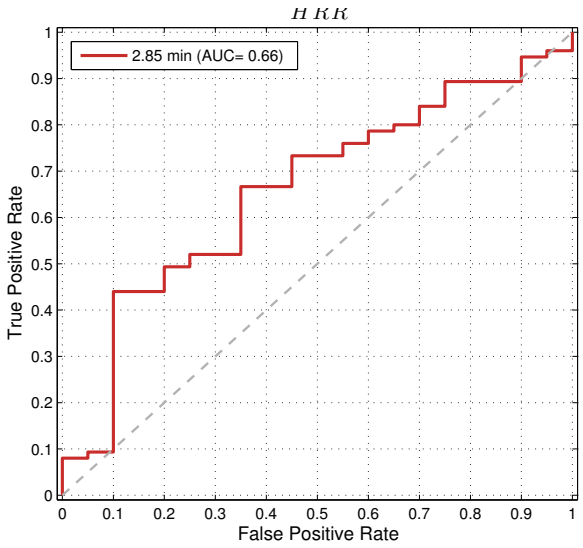

Figure 4. ROC curve corresponding to the values associated with the critical difference found between the symptomatic and asymptomatic groups.

References

[1] Sarkozy A, Paparella G, Boussy T, Casado-Arroyo R, Yazaki Y, Chierchia GB, Brugada J. The usefulness of the consensus clinical diagnostic criteria in Brugada syndrome. International Journal of Cardiology, 167, 2700-2704.

[2] Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T Kamakura S. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol, 2010; 56:1576–1584.

[3] Behar N, Petit B, Probst V, Sacher F, Kervio G, Mansourati J, Mabo P. Heart rate variability and repolarization characteristics in symptomatic and asymptomatic Brugada syndrome. Europace, 2016 euw224.

[4] Dumont J, Hernandez A, Carrault G. Improving ECG beats delineation with an evolutionary optimization process. Biomedical Engineering, IEEE Trans Biomed Eng, 2010; 57:607–615

[5] Freeman, JV, Dewey, FE, Hadley, DM, Myers, J, Froelicher, VF. Autonomic nervous system interaction with the cardiovascular system during exercise. Progress in cardiovascular diseases, 48(5), 342-362.

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