

Comparison of Methods to Measure Baroreflex Sensitivity in Brugada Syndrome

Mireia Calvo^{1,2,3}, Virginie Le Rolle^{1,2}, Daniel Romero^{1,2}, Nathalie Béhar⁴, Pedro Gomis^{3,5}, Philippe Mabo^{1,2,4}, Alfredo Hernández^{1,2}

¹ INSERM U1099, Rennes, France

² LTSI, Université de Rennes 1, Rennes, France

³ ESAII Dept, EUETIB, CREB, Universitat Politècnica de Catalunya, Barcelona, Spain

⁴ Service de Cardiologie et Maladies Vasculaires, CHU Rennes, Rennes, France

⁵ CIBER of Bioengineering, Biomaterials and Nanomedicine, Spain

Abstract

Baroreflex sensitivity (BRS) is a valuable index to assess cardiovascular autonomic control and therefore to provide prognostic evaluation in many cardiac diseases. Although several methods have been developed to noninvasively capture spontaneous BRS, they are difficult to compare and often provide conflicting results. In this study we analyzed different BRS estimates obtained from a clinical series of thirty-two patients diagnosed with Brugada syndrome. They took part in a standardized head-up tilt test in order to quantify the level of agreement between the following measures: (1) $BRS^{+/+}$ and (2) $BRS^{-/-}$ from sequence analysis, (3) $BRS-LF$, (4) $BRS-HF$, (5) $BRS-LHF$, (6) $BRS-TF$ and (7) $BRS-TF_{LF}$ from cross-spectral analysis and (8) $BRS-SD$. Measures resulting from the sequence method failed to provide results in many recordings and showed low agreement with the remaining methods based on intraclass correlation coefficient results. Assuming an age-associated reduction in BRS, which has been previously reported, the lowest Pearson's correlation coefficients came from sequence analysis results. Thus, among the analyzed BRS estimates, those derived from sequence analysis showed a lower reliability when capturing baroreflex function in Brugada syndrome patients.

1. Introduction

Brugada syndrome (BS) is a genetic disorder characterized by a distinctive ECG pattern with ST-segment elevation in anterior precordial leads, associated with an elevated risk for sudden cardiac death (SCD) due to malignant ventricular arrhythmias [1]. The autonomic nervous system (ANS) function plays an important role in the pathophysiology, arrhythmogenesis and prognosis of the disease. Indeed, cardiac events in BS typically occur at

rest and especially during sleep, thus being commonly associated with an increased vagal tone. Moreover, a number of studies have also shown an abnormal sympathetic innervation in this population that leads to an autonomic imbalance [2]. However, despite this rising evidence that BS prognosis significantly depends on autonomic imbalance, it is still unclear which autonomic tests and indicators yield the highest predictive value to identify BS patients at high risk of SCD.

The main objective of this work was thus to characterize the autonomic function of a set of patients suffering from BS by estimating their baroreflex sensitivity (BRS) during a standardized head-up tilt (HUT) test. However, the estimation of BRS may be difficult, especially during non-stationary conditions. We have thus calculated eight previously described BRS estimates in order to quantify their level of agreement and compare their robustness. Finally, these BRS estimates were used to compare symptomatic versus asymptomatic BS patients.

2. Methodology

2.1. Study population and data acquisition

Thirty-two patients diagnosed with Brugada syndrome (nine were symptomatic) took part in a HUT test while noninvasive blood pressure and ECG recordings were collected. After approval by the ethics committee of the Centre Hospitalier Universitaire de Rennes (CHU Rennes), all participants provided informed consent to participate in the study. Patients' age ranged from 20 to 79 years old (52.19 ± 14.74 years old) and 25 were males.

The test was divided into three phases: i) supine rest for 10 minutes, ii) tilting with an inclination of 60° for 45 minutes and iii) rest in supine position for 10 minutes.

ECG and blood pressure signals were acquired with the

Task Force Monitor (CN Systems, Graz, Austria) at a sampling frequency of 1000 Hz and 100 Hz, respectively. Each heartbeat and its associated systolic blood pressure (SBP) were detected as the maxima above a manually adjusted threshold. RR series were identified using a noise-robust wavelet-based algorithm for QRS complex detection and subsequent R-wave peak location [3]. Both RR and SBP series were manually corrected when necessary and, for frequency analysis, they were detrended, interpolated with cubic splines and regularly resampled at 4 Hz.

Since the BRS methods under study required stationary data, four 10-minutes segments from each recording were analyzed, leading to 128 BRS results for each method: i) in supine position before the test, ii) in upright position after 10 minutes of tilting, iii) in standing position after 20 minutes and iv) in supine position after tilting.

2.2. Baroreflex sensitivity

Several methods have been proposed to noninvasively estimate spontaneous BRS from variations in blood pressure and RR series. Since they are difficult to compare and often lead to conflicting results, previous works have already analyzed different BRS estimates in healthy subjects and different patient populations [4, 5]. In this work, we calculated and compared eight different BRS measures. Baroreflex function was firstly estimated using the sequence method for (1) positive ($BRS^{+/+}$) and (2) negative ($BRS^{-/-}$) sequences, considering three or more consecutive beats in which increasing/decreasing SBP values were followed by progressive lengthening/shortening in RR series [6]. Slopes of the regression lines relating positive/negative changes in both signals with a correlation coefficient higher than 0.8 were then averaged to obtain $BRS^{+/+}$ and $BRS^{-/-}$.

BRS estimates (3) $BRS-LF$, (4) $BRS-HF$ and (5) $BRS-LHF$ were calculated as the square root of the ratio of the autoregressive powers of RR and SBP series in the LF (0.04 - 0.15 Hz), HF (0.15 - 0.40 Hz) and simultaneously in both frequency bands (0.04 - 0.40 Hz) [7], respectively, when coherence between both series was greater than a threshold defined in Gallet et al [8]. Spectral power was obtained as the average of applying the Burg method with optimized order based on the Broersen's combined information criterion (CIC) [9] to 5-minutes intervals. Coherence was obtained from a Welch periodogram with a 50% overlap and Hanning windowing.

Based on the transfer function method, (6) $BRS-TF$ was extracted from the average gain of the transfer function ($|TF_{RR,SBP}|$) within the LF range [10], at frequencies of maximum coherence upon a threshold specified in [8]. However, since the coherence criterion has been shown to provide inaccurate BRS measurements when the baroreflex becomes strongly depressed, (7) $BRS-TF_{LF}$ was ob-

tained from the average of $|TF_{RR,SBP}|$ over the whole LF band, without considering coherence values [11].

Finally, (8) $BRS-SD$ was estimated as the standard deviation of RR divided by the standard deviation of SBP, when both series were previously detrended [4].

2.3. Statistical analysis

The level of agreement between methods was calculated using the intraclass correlation coefficient (ICC) and classified as low when $0 < r < 0.5$, medium when $0.5 < r < 0.7$ and high when $r > 0.7$.

Pearson's correlation coefficients (PCC) and associated p -values were calculated between BRS estimates in resting conditions and patients' age. The closer to -1 the PCC, the more confident the negative linear correlation between age and the BRS measure was considered.

Comparisons between symptomatic and asymptomatic patients were evaluated by Mann-Whitney U non-parametric tests for the different phases of the HUT test.

The analysis was made using the commercially available statistical program SPSS 21.0 (IBM, Chicago, USA) and setting the level of significance at $p < 0.05$.

3. Results

Upright posture during HUT testing causes a venous return reduction that stimulates a reflex increase in sympathetic activity and vagal inhibition, increasing heart rate and arterial blood pressure, and thus reducing BRS, by incrementing myocardial contractility and vascular resistance. Conversely, supine position provokes a systemic arterial pressure rise that activates arterial baroreceptors and leads to a drop in sympathetic activity and an increase in vagal tone, incrementing BRS [12].

Figure 1 represents the mean and 95% confidence interval of BRS estimates, calculated on each 10-minutes segment of the HUT test for the whole population. Considering the general tendency along the four segments under study, estimates typically decreased at the beginning of tilting, progressively incremented for the second standing phase and remained increasing after the test, without reaching baseline values. All methods captured a reduction in BRS after 10 minutes of tilting with respect to baseline, as well as an increase after the HUT test. However, $BRS^{+/+}$, $BRS^{-/-}$ and $BRS-SD$ still captured a reduction in BRS in the second segment of tilting, as well as $BRS^{+/+}$ detected a higher BRS recovery after the test with respect to baseline. Moreover, a strong variability in the results coming from the sequence method could be noted from the error bars.

Some BRS estimates are often impossible to calculate due to the properties of the observed RR and SBP series.

Table 1 shows, for each BRS estimate, the number of 10-minutes segments that could not be calculated (from the 128 available segments). BRS estimates resulting from the sequence method provided the highest numbers of missed values, whereas *BRS-SD* and *BRS-TF_{LF}* gave results in all cases. The resting methods using coherence as a parameter of quality had two or more missed values.

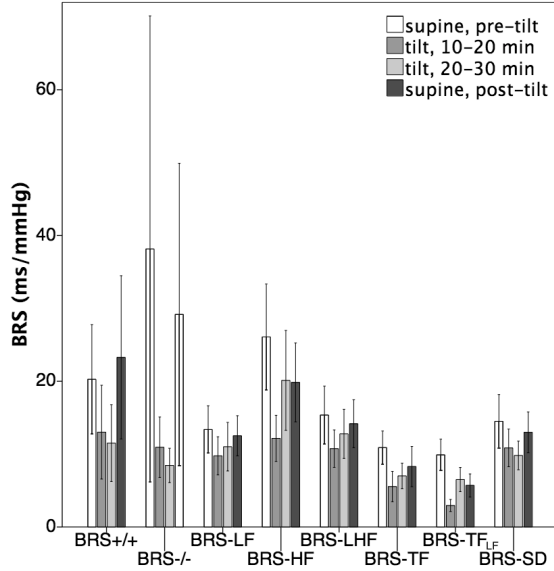


Figure 1. BRS estimates for each method and phase of the test.

Table 1. Missed values in 128 recordings.

BRS estimate	Missings
<i>BRS^{+/+}</i>	40
<i>BRS^{-/-}</i>	43
<i>BRS-LF</i>	9
<i>BRS-HF</i>	3
<i>BRS-LHF</i>	2
<i>BRS-TF</i>	25
<i>BRS-TF_{LF}</i>	0
<i>BRS-SD</i>	0

Table 2 presents results from the ICC analysis for all BRS estimates and for different phases of the HUT test. In supine position, estimations using the sequence method showed the lowest agreement, whereas *BRS-LF*, *BRS-LHF* and *BRS-SD* were in high accordance with the other methods. In standing position, *BRS^{-/-}* and *BRS-HF* were in low agreement, while *BRS-LHF* and *BRS-TF* were highly consistent with the other measures. When analyzing supine and standing positions conjointly, both results coming from the sequence method showed low accordance, whereas *BRS-LF*, *BRS-LHF* and *BRS-SD* were

in high agreement.

Assuming an age-associated reduction in BRS, which has been previously reported [13], Table 3 shows that the lowest correlation between age and BRS came from sequence analysis (*BRS^{+/+}*), whereas *BRS-LF* was the method showing the greatest correlation ($p = 0.002$).

Table 2. Mean \pm standard deviation of ICC for each method.

BRS estimate	Supine	Standing	Whole test
<i>BRS^{+/+}</i>	0.37 \pm 0.10	0.54 \pm 0.18	0.45 \pm 0.17
<i>BRS^{-/-}</i>	0.38 \pm 0.15	0.46 \pm 0.29	0.42 \pm 0.23
<i>BRS-LF</i>	0.73 \pm 0.24	0.69 \pm 0.20	0.71 \pm 0.22
<i>BRS-HF</i>	0.68 \pm 0.17	0.44 \pm 0.30	0.56 \pm 0.27
<i>BRS-LHF</i>	0.76 \pm 0.22	0.75 \pm 0.17	0.75 \pm 0.20
<i>BRS-TF</i>	0.69 \pm 0.28	0.70 \pm 0.26	0.69 \pm 0.27
<i>BRS-TF_{LF}</i>	0.59 \pm 0.29	0.53 \pm 0.30	0.56 \pm 0.29
<i>BRS-SD</i>	0.72 \pm 0.24	0.67 \pm 0.25	0.70 \pm 0.24

Table 3. Pearson's correlation coefficients (PCC) and associated p -values for each method.

BRS estimate	PCC	p -value
<i>BRS^{+/+}</i>	-0.015	0.953
<i>BRS^{-/-}</i>	-0.406	0.085
<i>BRS-LF</i>	-0.520	0.002*
<i>BRS-HF</i>	-0.325	0.074
<i>BRS-LHF</i>	-0.505	0.003*
<i>BRS-TF</i>	-0.490	0.005*
<i>BRS-TF_{LF}</i>	-0.505	0.003*
<i>BRS-SD</i>	-0.344	0.054

* $p < 0.05$ when comparing age and BRS.

Finally, Table 4 summarizes the associated p -values when comparing BRS parameters between symptomatic and asymptomatic patients. As in a previous study where Mizumaki et al [14] assessed the baroreflex function of BS patients through the invasive phenylephrine method, no significant differences related to symptomatology were found in BRS.

4. Conclusion

We analyzed eight different methods to measure BRS in thirty-two Brugada syndrome patients who underwent a standardized HUT test in order to compare and quantify the level of agreement and robustness between such measures. Although the assessment of the ANS function in BS is of major clinical importance, we ignore the existence of any study comparing spontaneous BRS estimates from a clinical series of patients suffering from BS.

Among the studied methods, those derived from sequence analysis showed a lower robustness when capturing baroreflex function. Although they allow for taking

Table 4. *P*-values when comparing symptomatic (n=9) and asymptomatic (n=23) BS patients.

	Supine, pre-tilt	Tilt, 10- 20 min	Tilt, 20- 30 min	Supine, post-tilt
<i>BRS</i> ^{+/+}	0.152	0.720	0.495	0.301
<i>BRS</i> ^{-/-}	0.898	0.354	0.194	0.425
<i>BRS-LF</i>	0.681	0.753	0.842	0.722
<i>BRS-HF</i>	0.842	0.642	0.520	0.363
<i>BRS-LHF</i>	0.967	0.520	0.774	0.509
<i>BRS-TF</i>	0.912	0.953	0.983	0.687
<i>BRS-TF_{LF}</i>	0.621	0.321	0.805	0.711
<i>BRS-SD</i>	0.902	0.386	0.742	0.934

into account the asymmetry of baroreceptor response by calculating distinct estimates for increasing and decreasing arterial pressure values, they can fail to provide results in many recordings when the needed requirements are not met. In contrast to the general tendency, *BRS*^{+/+} captured a continued decrease in BRS along the HUT test, as well as an increase after the trial, greater than baseline values. In addition, a large variability was found in this measure with respect to the rest of estimates. Results obtained from sequence method were in low agreement with the other techniques and, among all BRS estimates, they presented the lowest correlation with patients' age.

On the other hand, *BRS-LF* was a reliable measure of BRS in this clinical series. Although it also failed to provide some results, *BRS-LF* was in accordance with expected tendencies. It also showed a high level of agreement with the rest of measures.

When BRS was compared between symptomatic and asymptomatic patients, no significant differences were found along the HUT test. Although cardiovascular diseases often coexist with disabilities in baroreflex mechanisms, we identified no association between BRS values and symptomatic status in Brugada syndrome. However, these findings should be confirmed in a larger patient population.

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Address for correspondence:

Virginie Le Rolle
 LTSI, Université de Rennes 1,
 Campus Beaulieu, Bât 22, 35042 Rennes, FRANCE
 virginie.lerolle@univ-rennes1.fr