Cardiac autonomic control in Brugada patients during sleep: the effects of sleep disordered breathing

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Abstract

Aims—Brugada syndrome is characterized by typical ECG features, ventricular arrhythmias and sudden cardiac death (SCD), more frequent during nighttime. Autonomic cardiovascular control has been implicated in triggering the ventricular arrhythmias. Sleep-disordered breathing (SDB) elicits marked autonomic changes during sleep and it is associated with an increased risk of nighttime SCD. Brugada patients may have a higher likelihood of SDB compared to controls.

Address for correspondence: Virend K Somers Somers.Virend@mayo.edu Phone number: 507-255-1144, Fax number: 507-255-7070 Department of Cardiovascular Diseases Mayo Clinic, Rochester, MN, USA Autonomic control in Brugada syndrome during sleep.

However, no data are available on cardiac autonomic control in Brugada patients, particularly with regard to the comorbidity of SDB.

Methods—We evaluated autonomic cardiovascular control in Brugada patients with SDB (BRU-SDB, n=9), without SDB (BRU, n= 9), in controls (CON, n=8) and in non-Brugada patients with SDB (n=6), during wakefulness and sleep (N2, N3 and REM). Linear spectral and entropy-derived measures of heart rate variability (HRV) were performed during apnea-free stable breathing epochs.

Results—Total HRV was attenuated in BRU-SDB compared to CON and BRU. During N2 and REM, in BRU-SDB patients sympathetic modulation decreased compared to BRU and CON, while during REM, they showed an increased parasympathetic modulation, compared to the other two groups. BRU-SDB and SDB were similar in terms of spectral components. Entropy-derived indices showed preserved dynamic changes in Brugada patients compared to controls through the different sleep stages.

Conclusion—Brugada syndrome *per se* does not appear associated with an altered autonomic cardiovascular control during wakefulness and sleep. The comorbidity with SDB may contribute to disrupted autonomic cardiovascular regulation during sleep, possibly predisposing to the increased likelihood of sleep-related ventricular tachyarrhythmias and SCD.

Keywords

Brugada syndrome; sleep disordered breathing; heart rate variability; non linear analysis; sleep; autonomic nervous system

Introduction

Brugada syndrome is a genetic disorder characterized by a typical ECG pattern with ST elevation in right precordial leads and right bundle branch block. The clinical manifestations include syncope, spontaneous ventricular tachyarrhythmias and sudden cardiac death (SCD) [1]. Interestingly, the ventricular tachyarrhythmias and SCD occur predominantly during nighttime than daytime and during sleep compared to wakefulness [2].

It has been hypothesized that the autonomic nervous system (ANS) plays a key role in arrhythmogenesis in Brugada patients, with a predominant vagal modulation of heart rate variability (HRV) during night, associated with altered cardiac sympathetic activity [3]; these phenomena have been linked to the increased risk of cardiac arrhythmias and SCD in these subjects [4]. However, conflicting results have been reported: a presynaptic sympathetic alteration has been described [3], while analyses of HRV using 24-h ECG Holter revealed either altered HRV in Brugada subjects with ventricular fibrillation compared to controls [5,6], or no differences in HRV parameters between healthy subjects and Brugada patients [7].

In keeping with these inconsistencies, two recent papers [8, 9] highlighted the inadequacy of traditional markers of risk stratification to detect Brugada patients at higher risk for SCD, hence calling for evaluation of new risk stratifiers.

Sleep-disordered breathing (SDB) refers to a group of diseases characterized by intermittent episodes of apnea during sleep. These conditions have been strongly associated with marked changes in nocturnal neural circulatory control [10,11] and with increased cardiovascular morbidity and mortality [12-18]. Indeed, like Brugada syndrome, sleep apnea is accompanied by an increased risk of nocturnal SCD [19].

Recently, Macedo and colleagues showed that the prevalence of SDB is higher in Brugada patients compared to controls (45% vs 27% respectively) [20].

Different tools such as spectral analysis and entropy-derived indices have been applied to evaluate HRV during sleep in physiological and pathological conditions [21-25] and they can provide complementary information on neural mechanisms regulating cardiac sinus node function [26, 27].

To our knowledge, no data are available on the modifications of autonomic cardiovascular control in Brugada patients during the different sleep stages nor has the effect of comorbid SDB on sleep-related neural circulatory control been studied.

The aim of the present study was twofold: first, to evaluate cardiac autonomic control in Brugada syndrome patients with and without SDB; second, to assess the dynamic changes of autonomic regulation during the different sleep stages in these patients.

Methods

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [28].

Patients and control subjects are the same as in the study of Macedo et al. [20]. Subject characteristics have been previously reported. In the Brugada group, mean age was 50 ± 15 years, BMI was 24.7 ± 2.7 kg/m^2 and 75% of subjects were males.

Patients were diagnosed with Brugada syndrome according to established criteria [1]: 15 subjects had an abnormal baseline ECG and 5 subjects had an abnormal ECG after antiarrhythmic drug challenge with ajmaline or flecainide. Of the 20 patients with Brugada syndrome, 14 had experienced syncope and/or SCD at the time of diagnosis, while 6 patients had a history of SCD in one or more first degree relatives.

A diagnosis of SDB was made in 9 of 20 Brugada patients, while 11 showed a normal sleep study. Two Brugada patients without SDB were excluded due to the excessive supraventricular beats, thus precluding any HRV analysis.

Polysomnographic data

We recruited 20 consecutive patients evaluated at the Hospital Clinic, University of Barcelona. Inclusion criteria were age > 21 years and a definitive diagnosis of Brugada Syndrome. A complete polysomnographic (PSG) study was performed in all subjects. A control group of healthy subjects (CON, n=8) and a group of non-Brugada patients with SDB (SDB, n=6) matched for age, gender and BMI with the Brugada patients, were also studied. The study was approved by the IRB of the University of Barcelona and the Mayo Clinic (Rochester, Minnesota). Informed consent was signed by all participants.

Polysomnographic and autonomic testing laboratory at the University Hospital Barcelona was facilitated using the ANNAlab Portable Research Laboratory Technology (St. Anne's University Hospital Brno and Institute of Scientific Instruments of Czech Academy of Sciences, Brno, Czech Republic).

PSG studies were performed using a Compumedics Siesta 802 wireless amplifier/recorder (Compumedics, Abbotsford, Victoria, Australia). Electroencephalogram, electro-oculogram, electromyogram, ECG and respiration via oronasal thermal airflow sensor and respiratory impedance plethyismography were recorded continuously. The ECG was sampled at 512 Hz, and the respiratory signal at 32 Hz. Polysomnographic studies were scored by an expert

blind sleep technologist. The diagnosis of SDB was made if the apnea/hypopnea index (AHI) was 5 events/hour.

Data analysis

From the full polysomnographic recording, we extracted ECG and respiratory traces. These two signals were then divided into wakefulness (W), Non-REM sleep (N2 and N3) and REM sleep by merging the polysomnographic traces with the hypnograms (i.e. text files reporting the sleep scoring). Thus, we obtained segments of ECG and respiratory signals divided into W, N2, N3 and REM.

Analyzing the full sleep study, we considered the first two complete sleep cycles for each subject (a complete sleep cycle is defined by the presence of both NREM and REM sleep).

For Brugada patients diagnosed with SDB and non-Brugada SDB patients, we carefully avoided periods with apneas/hypopneas and we considered only ECG segments associated with stable and regular breathing.

For the autonomic analysis, from the ECG signal we constructed the time series of all the consecutive heart periods, the tachograms. Briefly, after the detection of QRS complexes, the apex of the R wave was located using a parabolic interpolation. QRS detection was checked to avoid missed beats and incorrect detection of R waves. The time series obtained, the tachograms, were linearly detrended. Consecutive samples of short segments of 250-300 beats were selected for spectral and entropy analyses, according to the different sleep stages among the four groups.

Respiratory traces were resampled at 512 Hz and the respiratory rate was assessed from the respiratory signal.

Assessment of cardiac autonomic control

Spectral analysis of HRV—Spectral analysis is a reliable and widely used tool to investigate autonomic oscillations encoded in the heart period time series. This analysis is based on an autoregressive model and is able to evaluate the rhythmic oscillations related to autonomic modulation in sinus node function [21-23; 27]. Three main components can be identified: a very low frequency component (VLF) (below 0.04 Hz), a low frequency component (LF) (bounded between 0.04-0.15 Hz), considered a marker of sympathetic modulation, and a high frequency component (HF), synchronous with respiration and considered a marker of vagal modulation. Each oscillation is described by a specific frequency band and amplitude. The amplitude of the LF and HF oscillations can be expressed in absolute units (ms^2) and in normalized units (nu). The nu represent the relative values of each spectral component, LF and HF, in proportion to the total power, calculated as follow: LF nu= [LF absolute units / (total power – VLF power)] and the HF nu = [HF absolute units / (total power-VLF)]. The ratio between LF and HF power was calculated (LF/HF), considered a marker of the sympatho-vagal balance.

Corrected Conditional Entropy (CCE) and Regularity Index—A complete description of the mathematical basis has been published elsewhere [25-26, 29]. Briefly, entropy-derived measures evaluate the complexity of important information on the complexity (or, its opposite, regularity) of the autonomic cardiac control. In fact, several mechanisms work together for the regulation of heart period function (i.e. central oscillators, chemoreflex and baroreflex pathways, sympathetic and parasympathetic modulation of the sinus node, etc). Decreased complexity (and increased regularity) represents a situation characterized by the predominance of one of the regulatory mechanisms involved to the

detriment of the others, leading the system less capable of properly responding to external stressor stimuli. Different measures have been used to assess autonomic cardiovascular complexity, and Regularity Index and Corrected Conditional Entropy (CCE) are two of the most common tools.

The definition of CCE is based on the definition of Conditional Entropy, CE, an index that assesses the amount of information carried by the current RR sample (i.e., RR(i)) when L-1 past samples of RR are known (i.e., $RR_{L-1}(i-1) =(RR(i-1), …, RR(i-L+1)))$. This index represents the difficulty in predicting the future values of a time series when the past values are known. Unfortunately the estimate of CE is biased and, thus, CCE was designed. CCE is bounded between 0 and the Shannon entropy, representing the maximum amount of information derived from the RR series.

The CCE decreases to 0 when the new sample is fully predictable, it is of maximum value when the new sample is unpredictable, and it is of minimum value when the knowledge of past values is helpful in reducing the uncertainty associated with future values. From this measure, an index of regularity, Ro, can be derived by dividing the CCE by the Shannon entropy. Ro ranges from 1 (maximum regularity, lowest complexity) to 0 (lowest regularity, maximum complexity).

Statistical analysis

Data are summarized as mean ± SE. SigmaPlot 11 (Systat Software Inc., Chicago, IL, USA) was used for the statistical analysis. A two-way ANOVA was performed to assess the differences between the groups within the sleep stages. The normality test was applied to check whether the distribution was normal. If this was not the case, the Equal Variance Test was performed. A Holm-Sidak method for all pair wise multiple comparison procedures was used. A $p<0.05$ was considered statistically significant.

Results

HRV analysis was performed in 9 Brugada patients without SDB (BRU), 9 Brugada patients with SDB (BRU-SDB), 8 controls (CON) and 6 non-Brugada SDB patients (SDB). Data are summarized in Tables 1.

Mean heart rate (HR) was similar among the four groups during W, N2 and REM, and higher during N3 in BRU-SDB and SDB compared to CON (p=0.017) and BRU (p=0.019). Considering the within-sleep stage analysis, HR during W was higher than during N2 (see Table. 1). Total variance decreased during Wake and REM in BRU-SDB and SDB patients compared to CON (p=0.02) and BRU (p=0.01) (see Fig. 2).

LFnu was lower during N2 and REM in BRU-SDB and SDB compared to BRU (p=0.02) and CON (p=0.01) (see Fig. 3). During REM sleep, HF nu was higher in BRU-SDB compared to BRU (p=0.012) and CON (p=0.001) (see Fig. 4). The non-Brugada SDB group did not significantly differ in terms of power spectral components from the BRU-SDB group.

Ro and CCE entropy measures showed no differences between the four groups during sleep stages. However, Ro was significantly different during N2 and N3 compared to W in BRU-SDB and BRU. In the CON group, Ro significantly changed in N3 compared to W and REM. Similarly, CCE changed during N3 compared to W in BRU-SDB and BRU and *also* compared to *REM* in CON *(see Figure 5)*.

No changes in respiratory frequency were observed between the three groups and within the different sleep stages.

There were no differences in terms of clinical manifestations and number of patients who received an implantable cardioverter-defibrillator (ICD) in the groups of Brugada patients. However, the electrophysiological study (EPS) was positive, i.e. able to induce VF, in 1 BRU patient without SDB and in 4 out of 9 BRU-SDB patients.

Discussion

The major findings of our study are first, that Brugada patients without co-morbid SDB have preserved neural control of HRV during wakefulness and sleep, while the presence of SDB is accompanied by altered neural cardiac regulation, namely an increase of vagal modulation more evident during REM sleep. Second, the dynamic changes in the complexity of neural control are similar in Brugada patients with and without SDB, in comparison with controls. These observations are of clinical significance, particularly with regard to stratifying Brugada patients at higher risk.

Brugada syndrome is associated with specific ECG characteristics and predisposes to VF, more frequent during night and sleep than wakefulness [2], while patients with the majority of heart diseases have the highest incidence of SCD during the early morning [30, 31].

The dominant vagal modulation that characterizes deep sleep could be an arrhythmogenic trigger in Brugada patients [4]. The key role played by the ANS has been shown in previous studies [3, 32-34].

The available data on HRV in Brugada patients are contradictory. Pierre et al [35] reported that 24-h ECG Holter of symptomatic Brugada patients were characterized by lower LF and HF components [6, 36], while other studies showed no differences in HRV between Brugada and healthy subjects, either during day or night [7]. When interpreting the contrasting results, several factors must be considered carefully: first, 24-h ECG Holter recordings do not differentiate between wake and sleep; second, comorbid (and often undiagnosed) SDB could potentially contribute to autonomic alterations; third, respiratory irregularities and apneas due to SDB would confound HRV measures; fourth, cardiovascular autonomic control is not stable during sleep, so it is essential to consider the different sleep stages. Moreover, the high prevalence of SDB in Brugada patients [20] may also contribute to the inconsistency in data. We therefore suggest a novel approach to these patients, taking into consideration SDB.

We showed that during sleep, total variability was lower in BRU-SDB patients compared to CON and BRU, was further reduced during REM sleep, accompanied by a decreased sympathetic modulation. A predominant vagal modulation was present in BRU-SDB during REM sleep, consistent with previous observations [4, 6].

We observed reduced total power associated with vagal predominance in BRU-SDB during REM sleep. One possible explanation is that REM sleep may be characterized by coactivation of the sympathetic and parasympathetic branches. While there is agreement in considering cardiac vagal modulation protective and sympathetic activation detrimental for cardiovascular control [36, 38], a coactivation of the two branches of the ANS may elicit a highly unstable electrophysiologic milieu, triggering life-threatening arrhythmias [39, 40]. This phenomenon may occur during apneas in patients with SDB [41, 42], when chemoreflex excitation is associated with simultaneous vagal and sympathetic activation. Therefore, our data suggest that in normal conditions, Brugada patients have preserved HRV control and a predominant vagal modulation, which could become a pro-arrhythmic

substrate in situations characterized by surges of sympathetic bursts such as apnea, more evident during REM sleep, a condition of potential risk factor for the cardiovascular system [26], when both vagal modulation in Brugada and sympathetic surges associated with apneas are greater.

In addition, it is conceivable that during REM, autonomic cardiac control is characterized by an increased cardiac vagal outflow from arterial baroreflex, which overpowers the concomitant peripheral (and cardiac) sympathetic activation, typical of REM sleep. This mechanism could also help explain the lack of an increase in HR despite sympathetic activation as previously reported in healthy subjects [43, 44].

An additional finding supporting this hypothesis relates to HRV total variance, a powerful tool to stratify the arrhythmic risk after cardiovascular events [45, 46]. In our study, Brugada patients had an overall variance similar to controls, while those with SDB showed significantly reduced variance both during wakefulness and sleep, as has been reported for patients with SDB [47]. SDB is associated with altered breathing patterns in sleep, with repetitive hypoxemic episodes causing frequent arousals during sleep. SDB is strongly related to an increased cardiovascular morbidity and mortality, and an impairment of autonomic cardiovascular control is thought to play a key role in this phenomenon [18]. We did not observe alterations of autonomic profile in Brugada syndrome, in contrast with previous studies [4-7]. However, this is the first study in which Brugada patients have been divided into two groups, with or without SDB, providing support for the hypothesis that comorbidity with SDB is the main contribution to altered autonomic control. Brugada patients without SDB and Controls showed a similar autonomic profile, supporting the concept that Brugada with and without SDB should be considered as two different populations in terms of autonomic regulation and thus, risk profile.

We further investigated the dynamic changes of autonomic control using complexity indices of HRV. A decreased complexity, or its opposite, an increased regularity, represent a situation characterized by the predominance of one of the regulatory mechanisms that collaborate to regulate sinus node function, leading the system to become less capable of properly responding to external stressor stimuli. It has been shown that different sleep stages are characterized by changes in the complexity of cardiac control, namely an increased CCE in slow wave sleep (N3) compared to Wake and REM, more evident in older subjects [26]. The present results confirm that complexity changes during different sleep stages, with a decreased regularity during slow wave sleep (N2 and N3) compared to Wake in all the groups and also compared to REM in Controls, and an increased CCE during N3 compared to Wake and also to REM in Controls. These observations suggest first, that the dynamic changes of complexity are similar in the four groups, with slow wave sleep characterized by lower regularity and higher complexity compared to Wake. Second, in Controls these changes are evident also compared to REM sleep, according to previous data, suggesting an autonomic control more capable of responding to external stressor stimuli during this stage.

These results might in part explain why traditional electrocardiographic markers of risk stratification failed to identify Brugada patients at higher risk for sudden cardiac death [8,9].

Interestingly, although BRU and BRU-SDB patients were similar in terms of clinical manifestations, we observed a difference in terms of induction of VF during EPS, being positive in 1 BRU and in 4 BRU-SDB respectively. Although this is a small population, we speculate that this observation may be of clinical relevance, considering that recent data suggest that EP testing may predict events in Brugada syndrome patients [48].

We therefore propose that screening for SDB in Brugada patients may provide important information for risk stratification. As our study was not designed to evaluate new markers,

prospective studies are required to properly assess the validity and reliability of the proposed measures in the Brugada population.

Study limitations

First, the small number of subjects in each experimental group could be responsible for the lack of significant changes of HRV parameters between the sleep stages despite clear trends.

However, it is worth noting that Brugada syndrome is a relatively uncommon disease among general the population, with a prevalence estimated at 5/10000. Nevertheless, we propose that Brugada patients need to be screened for SDB since this comorbidity may contribute to cardiovascular deregulation.

Second, a direct or indirect measure of peripheral sympathetic control such as MSNA or arterial blood pressure is lacking, since we limited our study to data acquired during sleep; in addition, for reasons of subject safety, we did not performed any pharmacological autonomic blockade in our subjects during sleep.

Finally, we consider the inducibility of VF at PVS as a surrogate index of "high risk patients", despite the fact that there is not yet consensus on this issue. However, screening for SDB in Brugada patients would be important, because this comorbidity, through impaired autonomic control, may possibly contribute to ventricular arrhythmias.

Conclusions

In conclusion, our data suggest that the presence of Brugada syndrome *per se* is not associated with an altered autonomic cardiovascular control during wakefulness and sleep, meaning that the abnormalities observed in Brugada patients cannot be fully explained by autonomic dysregulation. Both sleep apnea and Brugada syndrome are accompanied by an increased risk of nocturnal SCD. Therefore the strong comorbidity of Brugada syndrome with SDB may result in altered cardiac regulation, and possibly contribute to the pathogenesis of ventricular tachyarrhythmias and SCD. Although the present study does not aim to draw conclusive results on the mechanisms responsible for major cardiac events in Brugada syndrome, we believe that these data may help in better stratifying these patients in terms of risk profile.

Acknowledgments

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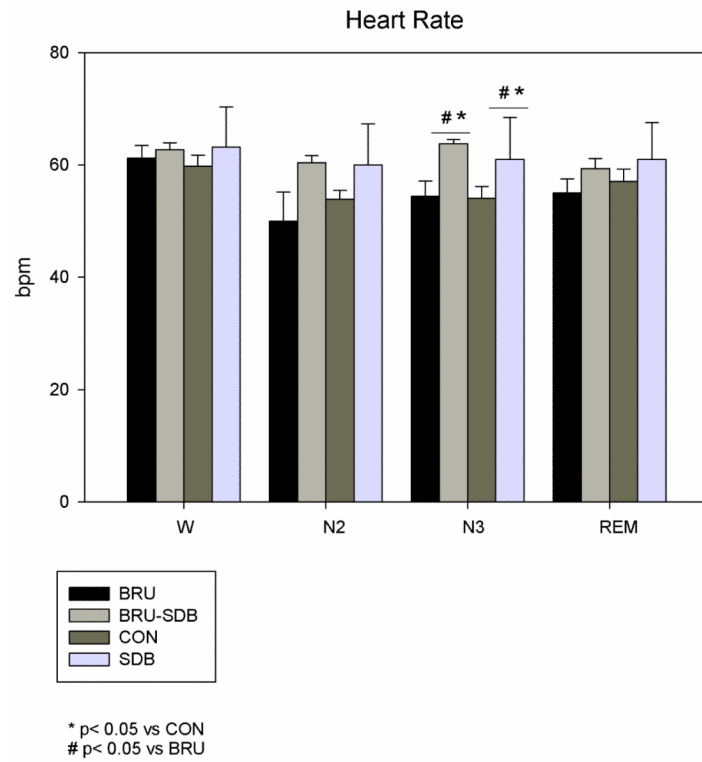
Figure 1.
Mean HR in BRU-SDB compared to BRU, CON and SDB during W and sleep. HR is higher in BRU-SDB and SDB compared to BRU and CON during N3.
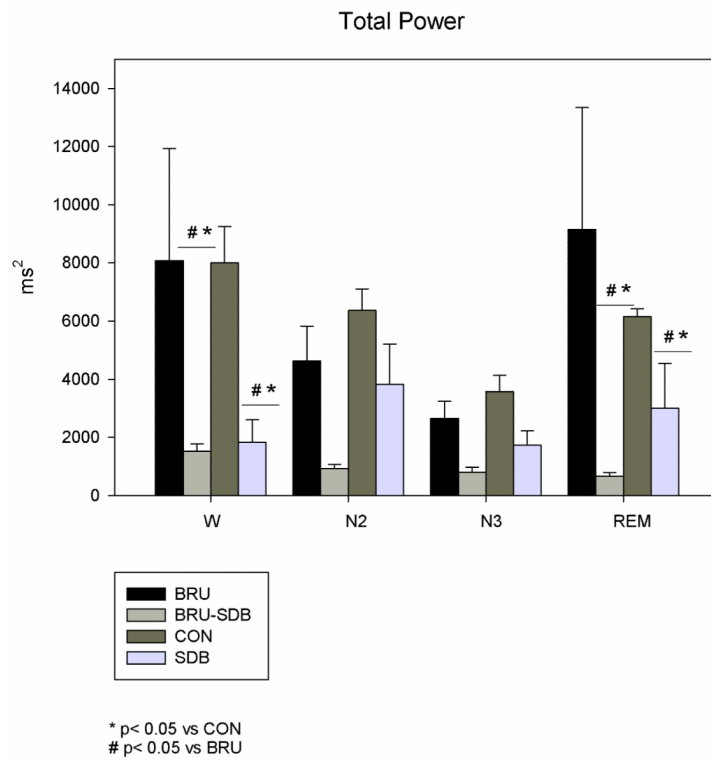
Figure 2.
Total power (TP) in BRU-SDB compared to BRU, CON and SDB during W and sleep. TP
is reduced in BRU-SDB and SDB compared to BRU and CON in all the sleep stages.
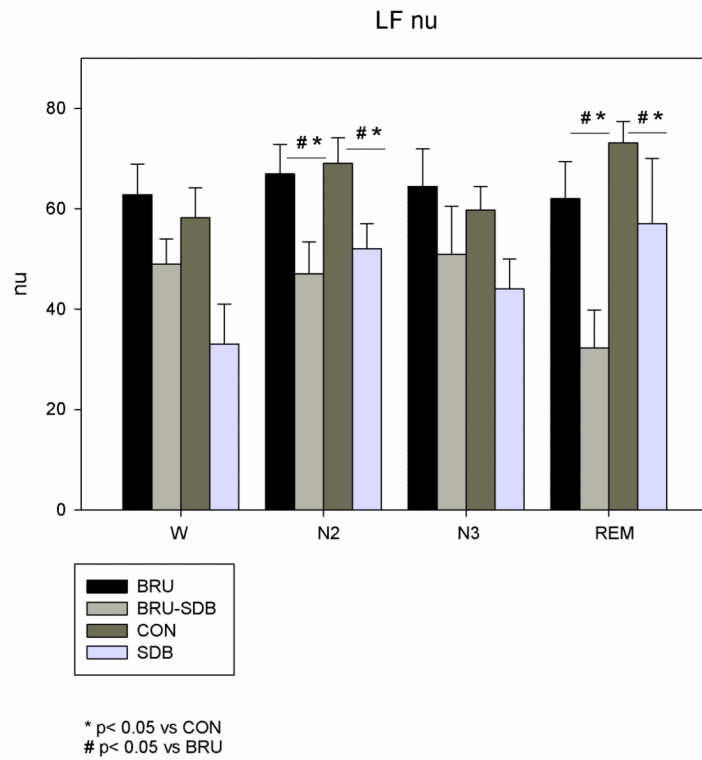
Figure 3.
LFnu in BRU-SDB compared to BRU, CON and SDB during W and sleep. LFnu decreased during N2 and REM in BRU-SDB and SDB compared to BRU and CON.
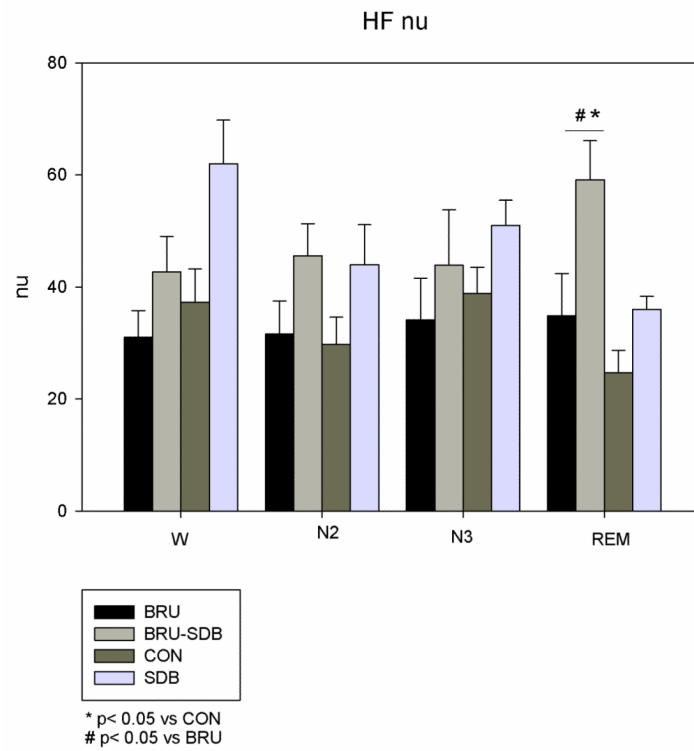
Figure 4.
HFnu in BRU-SDB compared to BRU, CON and SDB during W and sleep. HFnu increased in BRU-SDB and SDB compared to BRU and CON during REM sleep.
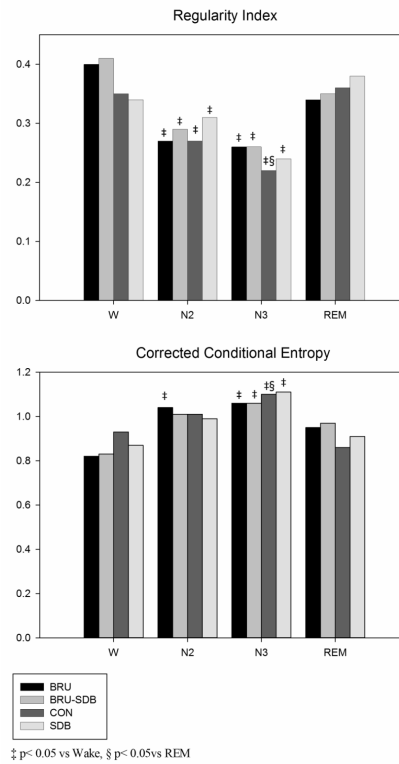
Figure 5.
Regularity Index and Corrected Conditional Entropy (CCE) during W and sleep in BRU, BRU-SDB, CON and SDB. Regularity Index is lower in N2 and N3 compared to Wake and also compared to REM in Controls. CCE is higher during N3 compared to Wake and also to REM in Controls.

Table 1

HRV during wakefulness and sleep in Brugada patients and control subjects

	Wake	N2	N3	REM
Heart Rate (bpm)				
Bru (n=9)	61 ± 2	54 ± 2[‡]	54 ± 3	55 ± 2
Bru-SDB (n=9)	63 ± 1	60 ± 1[‡]	64 ± 1[*,†]	59 ± 2
Con (n=8)	60 ±2	54 ± 1[‡]	54 ± 2	57 ± 2
SDB (n=6)	63±7	60±7	61±7[*,†]	61±6
Total power(ms²)				
Bru (n=9)	8077±3853	4627± 1191	2650±590	9157±4182
Bru-SDB (n=9)	1529 ± 254[*,†]	935 ± 142	798 ±177	662± 133[*,†]
Con (n=8)	7994 ±1254	6362 ± 740	3565±565	6152±268
SDB(n=6)	1838±768[*,†]	3824±1397	1731±506	3000±1552[*,†]
LF power (ms²)				
Bru (n=9)	3054±1500	2324 ± 509	1291±261	3220± 1441
Bru-SDB (n=9)	414±171	305 ± 90[*]	337 ± 82	1247± 63[†]
Con (n=8)	1608±241	3765± 596	1905±301	2834± 345
SDB(n=6)	463±266	2190±1038	818±209	1980±1188
HF power (ms²)				
Bru (n=9)	1219±674	809 ± 209	702 ± 234	1096±349
Bru-SDB (n=9)	137 ± 29	192 ± 27	217 ± 41	130 ± 19
Con (n=8)	1392± 825	1327±390	1094±307	814±249
SDB (n=6)	302±164	613±194	363±107	413±184
LF nu				
Bru (n=9)	63 ± 6	67 ± 6	64 ± 7	62 ± 7
Bru-SDB (n=9)	49 ± 5	47 ± 6[*,†]	51 ± 10	32 ± 7[*,†]
Con (n=8)	58 ± 6	69 ± 5	60 ± 5	73 ± 4
SDB(n=6)	33±8	52±9[*]	44±6	57±13
HF nu				
Bru (n=9)	32 ± 5	32 ± 6	34 ± 7	36 ± 7
Bru-SDB (n=9)	43 ± 6	46 ±6	44 ±10	59 ± 7[*,†]
Con (n=8)	37 ± 6	30 ± 5	39 ± 5	25 ± 4
SDB(n=6)	62±7	44±7	51±4	36±5[*]
LF/HF				
Bru (n=9)	4.2 ± 1.0	6.4 ± 2.1	4.7 ± 1.4	5.3 ± 1.7
Bru-SDB (n=9)	3.6 ± 1.1	2.2 ± 0.6	2.1 ± 0.8	1.5 ± 0.5
Con (n=8)	2.6 ± 0.5	4.7 ± 1.2	2.5 ± 0.5[§]	7.2 ± 1.7[‡]
SDB(n=6)	3.4±2.5	4±2.7	4±3.1	6±3.4

	Wake	N2	N3	REM
HF Hz Resp				
Bru (n=9)	0.27 ± 0.02	0.27 ± 0.03	0.27 ± 0.03	0.27 ± 0.04
Bru-SDB (n=9)	0.26 ± 0.01	0.24 ± 0.02	0.23 ± 0.02	0.24 ± 0.02
Con (n=8)	0.25 ± 0.03	0.23 ± 0.03	0.24 ± 0.03	0.24 ± 0.03
SDB(n=6)	0.27 ±0.01	0.25 ± 0.004	0.26 ±0.01	0.27± 0.01

Data are presented as mean ± SEM.

*
p< 0.05 vs CON

†
p<0.05 vs BRU

#
p<0.05 vs SDB

‡
p< 0.05 vs Wake

§
p< 0.05vs REM.