Clinical research

Heart rate variability in patients with Brugada syndrome in Thailand

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Aims Since patients with Brugada syndrome usually have symptoms at nighttime, we hypothesize that changes in autonomic modulation have an important role in the occurrence of the ventricular fibrillation episodes. The objective of this study was to determine the changes in heart rate variability (HRV) in patients with Brugada syndrome compared to asymptomatic subjects with Brugada ECG and controls.

Methods and results We studied 17 patients with Brugada syndrome, 10 asymptomatic subjects with Brugada ECG and 45 controls. Patients with Brugada syndrome and asymptomatic subjects with Brugada ECG underwent echocardiography, exercise stress testing, 24-h Holter monitoring, signal-averaged ECG. Patients with Brugada syndrome also underwent coronary angiography and electrophysiologic study. Time domain and frequency domain HRV analysis were performed at daytime and nighttime. The results of this study showed that patients with Brugada syndrome had lower HRV or lower vagal tone at night compared to the controls. They also had lower heart rate during the day and higher during the night compared to asymptomatic subjects and the controls.

Conclusion Patients with Brugada syndrome had low heart rate variability at night which may predispose to the occurrence of VF episodes.

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KEYWORDS
Heart rate variability; Brugada syndrome; Autonomic nervous system; Sudden unexplained death syndrome

Introduction

Sudden unexpected death syndrome (SUDS) is a common cause of death in young healthy Thai men. It is estimated that its prevalence is 26–38 per 100 000 population.1,2 It usually occurs at nighttime. Typically, the patients suddenly wake up having difficulty breathing, groaning, agonal respiration followed by cardiovascular collapse and death. However, some of them spontaneously recovered, and some reached the local hospital in time for medical assistance. The electrocardiogram (ECG) during attack usually showed ventricular fibrillation.3–5 The Center of Disease Control has reported the occurrence of sudden unexpected cardiac arrest in young male Southeast Asian refugees in the United States.6,7 A large proportion of SUDS survivors showed right bundle branch block (RBBB) with ST segment elevation8 which is similar to what has been described as Brugada syndrome by Pedro Brugada et al.9 Since the patients with Brugada syndrome usually have symptoms leading to cardiac arrest at night, we hypothesize that changes in autonomic modulation may have an important role in the occurrence of VF episodes at night in patients with Brugada syndrome. There have been little data on the study of diurnal pattern of autonomic modulation in these patients.

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The objectives of this study were to determine the difference in heart rate variability, the index of autonomic modulation, in patients with Brugada syndrome compared to asymptomatic subjects with Brugada ECG and controls.

Methods

Study population

We studied 17 men with Brugada syndrome who were referred for further management at Siriraj and Bhumijol Adulyadej Hospital. Nine patients presented with sudden cardiac arrest with documented ventricular fibrillation whereas eight patients had similar symptoms but no documented ventricular fibrillation. Brugada ECG is defined as right bundle branch block and ST segment elevation with J point elevation of ≥1 mV in leads V1–V3. We also studied 10 asymptomatic men with Brugada ECG detected during physical checkup or preoperative evaluation, and 45 healthy men as controls with normal 12-lead ECG. All patients and controls had no evidence of structural heart disease from history and clinical examination. All controls had normal beats at least 99% of total QRS complexes from 24-h ambulatory ECG monitoring, and were studied during the time of enrolment of patients with Brugada syndrome and asymptomatic subjects with Brugada ECG. We excluded patients with structural heart disease, long QT syndrome or cardiac arrest with identifiable causes, coronary artery disease, congestive heart failure or drug induced arrhythmia. This study was approved by the ethical committee of Siriraj Medical School, Mahidol University. Informed consent was obtained prior to participation.

Study protocol

All patients with Brugada syndrome and asymptomatic subjects with Brugada ECG underwent Doppler echocardiogram, exercise stress test using modified Bruce protocol, 24-h Holter monitoring, signal-averaged ECG (SAECG). Patients with Brugada syndrome also underwent cardiac catheterization including coronary angiography and electrophysiology study. Holter monitoring was performed in controls.

Electrophysiologic study

Electrophysiologic study was performed under sedation. Ventricular stimulation was first performed at right ventricular apex at three running cycle length: 600, 500 and 400 ms and up to triple ventricular extrastimuli at twice the diastolic current threshold. If there was no inducible ventricular tachyarrhythmia, the protocol was then repeated at right ventricular outflow tract position.

Signal-averaged ECG

The late potentials by signal-averaged ECG were analysed using Arrhythmia Research Technology 1200 EPX signal-averaged ECG system (Austin, Texas, USA). The analysis was based on the quantitative time domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. The QRS complexes at least 200 beats were amplified, digitized, averaged and filtered with a high pass filter (40 Hz). Three parameters were assessed using a computer algorithm: (1) the filtered QRS duration (f-QRS); (2) the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS40); and (3) the duration of low-amplitude signals <40 μV in the terminal filtered QRS complex (LAS40). In this study, the positive late potential was defined as at least two of the following criteria: f-QRS >114 ms, RMS40 <20 μV, and LAS40 >38 ms.

Ambulatory ECG monitoring

A 3-channel ECG monitoring was performed in each patient for 24-h period. A Zymed digital recorder was used to obtain the ECG data. Electrodes were attached at five different positions for the standard EASI lead system. All patients were free of effect of medication during ambulatory ECG monitoring. Patients were instructed to press the event button if they had symptoms such as palpitation, chest pain, or fainting so that the ECG playback would automatically display the ECG at that time. All patients kept a detailed diary recording the time of each episode of symptoms. Tapes were analysed with the Zymed system (Camarillo, California, USA). The analogue to digital sampling rate was 175 per second. The sampled ECG data were transformed from the Zymed scanner to a microcomputer for processing HRV. The ECG data were scanned and all QRS complexes were classified under the computer program. The accuracy of QRS complex detection and the label of QRS complexes were reviewed and manually edited by an experienced cardiologist. The QRS complexes were carefully classified into sinus beats, supraventricular or ventricular ectopic beats or artifacts or unclassified. The frequency histogram of the normal RR interval was displayed and the ECG of the intervals in both tails of the normal RR distribution was reviewed. Time domain variables and average heart rate were obtained from the 24-h ECG data. Time domain variables included standard deviation of all normal RR intervals (SDNN), average of standard deviation of normal RR intervals every 5 min (ASDNN). Frequency domain variables of the HRV were obtained by using fast Fourier transformation throughout the ECG recording. This technique was first described by Albrecht and Cohen and modified by Rottmen et al. For each Holter recording the sampling interval was 329 ms. A low pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines. A fast Fourier transformation was computed every 5 min for the whole dataset and the resulting power spectrum was corrected for the attenuating effects of both the filtering and sampling.

We computed the 24-h power spectral density and calculated the power within two frequency bands (1) low frequency power, 0.04–0.15 Hz, which reflects modulation of sympathetic and parasympathetic tone by baroreflex activity (2) high frequency power, 0.15–0.40 Hz, which reflects modulation of vagal tone and calculated total power spectrum.

Statistical analysis

Comparison of the three groups (Brugada syndrome, asymptomatic subjects with Brugada ECG, and controls) were made by ANOVA test with LSD post hoc analysis (least significant difference is a statistical method to explore which of the three pairs causes overall significant difference from ANOVA. LSD is calculated from the standard error of the difference between two means and the 5% value of t. The difference between a specific pair of means is significant at the 5% level if it exceeds the LSD value). Frequency domain variables (total power spectrum, low frequency power and high frequency power) were logarithmically transformed prior to analysis due to the non-normality of the data. The basic assumptions of the ANOVA of normality and constant variance of the residuals were satisfied. Continuous
data were described by mean and standard deviation and categorical variables were described by frequencies and percentages. Data for the whole 24 h, during daytime (08:00–20:00), and nighttime (00:00–06:00) were compared. Differences between daytime and nighttime results were calculated and compared between groups. \( P \) values ≤0.05 were considered significant. Although there were multiple comparisons for the results of this study, the parameters in which we are most interested are heart rate variability and vagal modulation at night since the episodes usually occur at nighttime.

Sample size calculation for the one-way ANOVA was performed by Power Analysis and Sample Size (PASS) program (Number Cruncher Statistical Systems, Kaysville, Utah, USA). We focused on what we are most interested in, which is high frequency power during the night and used data from the pilot patients and previous data from controls and assumed that data of asymptomatic subjects with Brugada ECG were somewhere in the middle. With the ratio of control:patient being 3:1, alpha 0.05, and beta 0.2, the target number of controls was 45 and that of patients in each group 15.

Results

All patients and controls were men. The average age was 41.6±6.9 years in Brugada syndrome, 35.8±9.3 years in asymptomatic subjects with Brugada ECG and 36.7±9.3 years in controls (\( P = 0.113 \) by ANOVA test). Nine out of 17 patients (53%) in symptomatic group had documented ventricular fibrillation during the attack but were successfully resuscitated and completely recovered. Eight patients had similar symptoms without documented ventricular fibrillation and were spontaneously recovered. Symptoms occurred between 18:00 to 06:00 in 14 patients (82.4%), mostly during sleep. All patients were found to have RBBB with ST segment elevation using the conventional 12-lead ECG after the episodes (Fig. 1). Baseline characteristics are shown in Table 1. All patients were not on any medications before referring to us except for one patient who was on a beta blocker. However, the drug was discontinued for the duration of at least five half-lives before ambulatory ECG monitoring and electrophysiologic study. Nobody had an implantable cardioverter-defibrillator. The physical activity was similar among the three groups and nobody involved in heavy athletic activities.

There was no evidence of structural heart disease from Doppler echocardiogram and no evidence of myocardial ischaemia on exercise stress test. Coronary angiography revealed no evidence of coronary artery disease and ventriculogram showed no evidence of left ventricular dysfunction in all patients. Electrophysiologic study showed inducible ventricular fibrillation or polymorphic ventricular tachycardia in 14 out of 17 patients (82.4%) with Brugada syndrome. Only two asymptomatic subjects with Brugada ECG underwent electrophysiologic study which was non-inducible in both.
SAECG showed late potentials in seven out of 17 patients (41.2%) with Brugada syndrome. Late potentials were positive in only one out of 10 asymptomatic subjects with Brugada ECG (10%) ($P=0.087$ by chi-square test).

Results of 24-h Holter monitoring and heart rate variability analysis

Holter monitoring showed only a few premature ventricular and premature atrial complexes which were of no statistical significance among the three groups. Table 2 showed results of heart rate variability analysis and comparison among the three groups. There were significant differences in average heart rate, ASDNN, SDNN, total power spectrum, low frequency power and high frequency power at nighttime between patients with Brugada syndrome in comparison to controls which meant that patients with Brugada syndrome had lower heart rate variability or lower vagal tone at night compared to controls. Heart rate variability parameters in asymptomatic patients were similar to the controls. To avoid multiple comparisons we did not analyse the normalized unit of the power spectral density. It has been shown in

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=45)</th>
<th>Brugada Syndrome (n=17)</th>
<th>Asymptomatic subjects with Brugada ECG (n=10)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average HR</td>
<td>75.0±8</td>
<td>70.0±13</td>
<td>74.5±5</td>
<td>0.157</td>
</tr>
<tr>
<td>Average HR (d)$^a$</td>
<td>81.6±9</td>
<td>72.8±12</td>
<td>81.3±6</td>
<td>0.006</td>
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<tr>
<td>Average HR (n)$^b$</td>
<td>60.1±7</td>
<td>66.7±12</td>
<td>59.7±6</td>
<td>0.024</td>
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<tr>
<td>ASDNN</td>
<td>65.0±21</td>
<td>55.5±21</td>
<td>64.4±19</td>
<td>0.268</td>
</tr>
<tr>
<td>ASDNN (d)</td>
<td>55.3±18</td>
<td>50.5±21</td>
<td>52.9±12</td>
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<tr>
<td>ASDNN (n)</td>
<td>80.3±27</td>
<td>61.6±24</td>
<td>80.0±27</td>
<td>0.043</td>
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<td>SDNN</td>
<td>162.5±48</td>
<td>105.7±28</td>
<td>162.8±42</td>
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<td>SDNN (d)</td>
<td>106.6±37</td>
<td>91.1±29</td>
<td>102.3±25</td>
<td>0.286</td>
</tr>
<tr>
<td>SDNN (n)</td>
<td>117.2±35</td>
<td>94.3±20</td>
<td>116.6±35</td>
<td>0.045</td>
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<tr>
<td>Total power</td>
<td>3.58±0.3</td>
<td>3.42±0.3</td>
<td>3.58±0.2</td>
<td>0.116</td>
</tr>
<tr>
<td>Total power (d)</td>
<td>3.41±0.3</td>
<td>3.35±0.3</td>
<td>3.39±0.2</td>
<td>0.798</td>
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<td>Total power (n)</td>
<td>3.75±0.3</td>
<td>3.53±0.3</td>
<td>3.76±0.2</td>
<td>0.021</td>
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<tr>
<td>LF</td>
<td>2.93±0.3</td>
<td>2.69±0.4</td>
<td>2.91±0.3</td>
<td>0.034</td>
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<td>LF (d)</td>
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<td>2.64±0.4</td>
<td>2.79±0.3</td>
<td>0.190</td>
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<td>LF (n)</td>
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<td>HF</td>
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<tr>
<td>HF (d)</td>
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<td>HF (n)</td>
<td>2.86±0.4</td>
<td>2.58±0.3</td>
<td>2.98±0.4</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Average HR=average heart rate (bpm); ASDNN=average of standard deviation of normal RR intervals (ms); SDNN=standard deviation of normal RR intervals (ms), Total=logarithmic transformation of the total power spectrum (ms²), LF=logarithmic transformation of the low frequency spectrum (ms²), HF=logarithmic transformation of the high frequency spectrum (ms²).

$^a$d=day.

$^b$n=night.
many previous studies that the non-normalized data is good enough for the prognostic indicator of sudden death both in patients with heart disease and in the general population. However, if we focus on the vagal tone or high frequency power at night and look at the comparison of the normalized unit, the finding remains significant (16.3% in controls, 11.6% in Brugada syndrome patients and 17.6% in asymptomatic subjects with Brugada ECG, \( P = 0.032 \) with significant difference between patients with Brugada syndrome to the other two groups). Patients with Brugada syndrome had lower heart rate variability at night than asymptomatic subjects with Brugada ECG but statistical analysis showed significant difference only in some parameters because of the relatively small sample size in asymptomatic patients. Patients with Brugada syndrome had significantly lower average heart rate during the day and higher during the night compared to asymptomatic subjects with Brugada ECG and controls. The difference in average heart rate between day and night was significantly smaller in patients with Brugada syndrome compared to asymptomatic subjects with Brugada ECG and the controls (6.2±2.9 vs 21.6±6.6 and 21.5±7.6, \( P < 0.001 \)). Fig. 2 and Fig. 3 showed 24-h SDNN and heart rates in a patient with Brugada syndrome compared to a control.

Discussion

SUDS in Thailand is called ‘Lai Tai’. It has been named differently in southeast Asian. Most patients who experienced SUDS are young men with a male to female ratio of 20:1. It has been reported that 68% of SUDS deaths occur between 21:00 to 04:00. Death is usually preceded by choking or gasping respiration, unresponsive and difficult to arouse, and usually occurs within minutes. It has considerable socioeconomic impact since it strikes the young men who are the heads of the family. It has been reported that SUDS is hereditary but little is known how the syndrome is passed. Approximately one-third of SUDS victims had relatives who had the similar pattern of death. Nademanee et al. reported that 59% of patients with SUDS had RBBB and ST segment elevation similar to that described by Brugada et al. SUDS survivors who had Brugada pattern ECG had worse prognosis than those without. Little is known why the symptoms of patients usually occur at night. This is different from sudden death episodes in patients with a structural heart disease which increases during early morning and is proposed to be related to the sympathetic surge in the morning hours. Changes in the autonomic modulation may play an
important role in the occurrence of such episodes. Some thought that increased vagal tone at night may have a deleterious effect and trigger the episodes. Van den Berg et al. reported a bradycardic cardiac arrest in patients with Brugada syndrome. Isoproterenol has been demonstrated to normalize an ST elevation and an increase in vagal activity can cause an ST segment elevation. Miyazaki et al. reported that an ST segment elevation in patients with Brugada syndrome is decreased by administering isoprenaline or acetylcholine and increased with propranolol or prazosin. They concluded that dysfunction of the autonomic nerves is an important modulator but not the primary disorder. These findings raise the concern of the use of beta-blocker in this group of patients. Changes in autonomic modulation may be an important factor for the selection of the appropriate management strategies of SUDS victims especially in Thailand where most patients cannot afford the internal defibrillator. If a high vagal tone is dangerous to patients then beta blockers which are an excellent drug for the prevention of sudden death in coronary artery disease patients may have a deleterious effect in SUDS victims and should not be used. Kasanuki et al. found that there was an increased in the vagal tone from the heart rate variability analysis of the ambulatory ECG recording before the episode. However, the episodes that were detected by the implanted cardioverter-defibrillator in these patients showed no evidence of bradycardia-dependence and in many cases the rate preceding the ventricular fibrillation episode was relatively fast. Leenhardt et al. observed abnormalities in the autonomic nervous system in 14 patients with idiopathic ventricular fibrillation that the heart rate variability was globally depressed especially the vagal component and lower day-to-night heart rate ratio which is consistent with findings in our study.

We demonstrated that there was no evidence of increased vagal tone at night in these patients compared to the controls. Instead, the symptomatic patients had a decreased heart rate variability during the night and smaller changes in the heart rate between daytime and nighttime. This may be one contributing factor to the occurrence of VF at night and vagal tone may not be dangerous to these patients. An increased vagal tone has been known as a protective factor against ventricular fibrillation and impaired vagal tone is associated with a decrease in the ventricular fibrillation threshold. Increased sympathetic activity together with decreased vagal tone during exercise may predispose to ventricular fibrillation especially in patients with structural heart diseases. The pathogenesis of ventricular fibrillation in patients with Brugada syndrome may be different from those with structural heart diseases. It may be multifactorial and may not be sympathetic dependent. In fact, Nimmanit et al. postulated that it might be related to the exaggeration of the normal nocturnal disturbance.
in potassium homeostasis. Sleep disturbance has been proposed by others.\(^{28}\)

One might question why low frequency power at night is lower in Brugada patients than in controls. Low frequency power is influenced by both sympathetic and vagal tone and is not a reliable marker for either sympathetic or vagal activity. Decreased low frequency power is commonly seen in patients with low heart rate variability and associated with a decrease in total power spectrum and high frequency power. It has been shown that not only a decrease in high frequency power but a decrease in low frequency power as well is a predictor of sudden death.\(^{14,15}\)

What we have learned from this study is that beta blocker may not be dangerous as previously thought. Implantable cardioverter-defibrillator is still the best treatment for those who already developed ventricular fibrillation. For those who cannot afford an internal cardioverter-defibrillator, it is uncertain what medication we can offer. We do not have enough evidence to recommend amiodarone. Beta blocker usage was supported by Nademanee et al.\(^{29}\) This study compared internal cardioverter-defibrillator and beta-blockers in patients with an unexplained death syndrome in Thailand which is a similar group of patients. Brugada ECG was demonstrated in 59% of patients in this study. The main finding is that internal cardioverter-defibrillator is better than beta-blockers. An interesting finding is that the event rate was twice in the defibrillator group compared to beta-blockers (20% vs 10% per year). Moreover, in eight patients who were randomized to a defibrillator and had frequent defibrillation shocks and were subsequently treated with beta-blockers, beta-blockers prevented recurrent ventricular fibrillation in patients and drastically suppressed the ventricular fibrillation episodes in three patients.

Brugada et al initially reported that asymptomatic subjects with Brugada ECG have the same risk of arrhythmic events as symptomatic patients.\(^{30}\) Two larger cohorts recently described that asymptomatic subjects had a much lower chance of the occurrence of sudden death comparing to symptomatic patients.\(^{31,32}\) In our study, we demonstrated that asymptomatic subjects with Brugada ECG had similar patterns of heart rate variability as controls and different from those of symptomatic patients. We cannot exclude age as a factor for the development of symptoms since asymptomatic cases in our study are slightly younger than symptomatic cases. However, based on the data from two long-term follow-up studies, average ages were similar for the asymptomatic group and the aborted sudden death group.

In conclusion, patients with Brugada syndrome had a lower heart rate variability at night compared to controls and asymptomatic patients. This may be a predisposing condition to the occurrence of ventricular fibrillation episodes at night in patients with Brugada syndrome.

Acknowledgements

This study was carried out at Siriraj Hospital, Bangkok, Thailand.

References


