Original Article

Autonomic and cardio-respiratory responses to exercise in Brugada Syndrome patients

Raoyrin Chanavirut, MSc[a,b], Pattarapong Makarawate, MD[c], Ian A. Macdonald, PhD[d], Naruemon Leelayuwat, PhD[b,e],*

[a] Medical Physiology Program, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand
[b] Exercise and Sport Sciences Research and Development Group, Khon Kaen University, Khon Kaen 40002, Thailand
[c] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand
[d] School of Life Sciences, Faculty of Medicine and Health Sciences, The University of Nottingham, Nottingham NG7 2UH, United Kingdom
[e] Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

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ABSTRACT

Background: Imbalances of the autonomic nervous (ANS), the cardiovascular system, and ionics might contribute to the manifestation of The Brugada Syndrome (BrS). Thus, this study has aimed to investigate the cardio-respiratory fitness and the responses of the ANS both at rest and during a sub-maximal exercise stress test, in BrS patients and in gender-matched and age-matched healthy sedentary controls.
Methods: Eleven BrS patients and 23 healthy controls were recruited in Khon Kaen, Thailand. They performed an exercise test on a cycle ergometer, and during the exercise, expired gas samples and electrocardiograms were collected. Blood glucose and electrolyte concentrations were analyzed before and after exercise. Then the heart rate variability (HRV) and the heart rate recovery (HRR) were analyzed from the electrocardiograms.
Results: The BrS patients showed a higher parasympathetic activation during exercise recovery than baseline. They had a smaller level of sympathetic activation during the period of exercise recovery than the controls did. They also showed a significantly lower peak HR, HRR, and peak oxygen consumption than the controls ($p < 0.05$). All subjects had a significantly lower percentage of peak oxygen consumption and respiratory exchange ratio during low-intensity ($p < 0.01$) and moderate-intensity ($p < 0.05$) exercise than during high-intensity exercise. The BrS patients had mild hyperkalemia which is reduced according to the exercise.
Conclusion: Thai BrS patients had a more rapid rate of restoration of the parasympathetic and smaller level of sympathetic activation after exercise. They had mild hyperkalemia which is reduced according to the exercise. Furthermore, they exhibited impaired cardio-respiratory fitness.

1. Introduction

Brugada Syndrome (BrS) is an autosomal dominant disease with incomplete penetrance that may cause syncope and sudden cardiac death (SCD) in young individuals with structurally normal hearts [1]. In Thailand, the annual death rate has been previously reported to be 26–38 per 100,000 young Thai men in the age range of 20–49 years old [2]. Previous studies proposed that the circadian variation or imbalance of the autonomic nervous system (ANS), assessed by evaluating the heart rate variability (HRV), and also other cardio-respiratory factors might contribute to the manifestation of the syndrome [1,3–4]. In addition, channel mutations in the cardiac myocytes including the potassium, sodium, and calcium channels were reported to be related to ventricular fibrillation (VF) which is attributed to an imbalance of the ANS [5,6]. However, the relationship of electrolyte changes and

ANS activity responses related to exercise has not been previously investigated. In addition, cardio-respiratory fitness, determined by peak oxygen consumption ($\dot{V}O_{2\text{ peak}}$), was reported to be strongly and inversely related to heart failure [7]. Therefore, $\dot{V}O_{2\text{ peak}}$ may reveal different levels of cardio-respiratory fitness in patients with Brugada Syndrome. However, until now, no research investigating $\dot{V}O_{2\text{ peak}}$ in the BrS has been performed.

In order to complement knowledge about the syndrome, this study aimed to investigate the responses of the ANS and cardio-respiratory system when at rest and in response to graded exercise in male patients with BrS and age-matched healthy sedentary men. The hypothesis of this study was that male BrS patients would present different autonomic and cardio-respiratory responses both at rest and in response to graded exercise when compared to age-matched healthy sedentary men.

2. Methods

2.1. Study design

This was a physiological study comparing BrS patients and control subjects. The BrS patients were recruited from the Outpatient Unit at the Queen Sirikit Heart Center of the Northeast in Khon Kaen, Thailand.

2.2. Study population

Eleven BrS patients and 23 age-matched healthy sedentary control subjects were recruited. The inclusion criteria for the patients were as follows: (1) being a male, (2) being between 18 and 60 years of age, (3) having survived sudden cardiac event which had led to the diagnosis of BrS, (4) having an implanted cardioverter-defibrillator (ICD), (5) having no structural heart disease (confirmed by ECG, transthoracic echocardiogram, and coronary angiogram), (6) having no coronary artery disease (confirmed by coronary angiogram), (7) having no manifest sick sinus syndrome and (8) being stable in physical and clinical status, as well as being alert (confirmed by a cardiologist).

The controls who were recruited from Khon Kaen Province in Thailand, had no history of heart, renal, or metabolic diseases and no family history of sudden unexplained death. They were matched to patients for age and gender and to those who did not exercise regularly. The subject's body composition was measured in the supine position by Dual emission X-ray absorptiometry (DXA). This study has been approved by the Ethical Committee of Khon Kaen University, according to the Declaration of Helsinki in 1995 (HE 541262).

2.3. Study protocol

On the day the experiment was conducted, all subjects visited the Nutrition and Exercise Laboratory at the Faculty of Medicine at Khon Kaen University at 7:00 AM. The subjects had all fasted overnight and had abstained from smoking, and from the consumption of caffeine and alcohol on the day before the visit. In addition, they had not performed any strenuous exercise for 2 days before the visit. Then they rested in a supine position for 60 min, and the ECG was recorded using LabChart® version 6 (AdInstruments, Australia) in order to evaluate the HR and HRV parameters. The ECG electrodes were used with the three-leadwire system (three electrodes pad and three leadwires (MCL4)) [8]. Next, a graduated multi-stage exercise test using an electromagnetically braked cycle ergometer (Corival, Lode, The Netherlands) was performed. The exercise test began with 3-min free load warm up at 50 rpm. After that, the starting workload was 30 W for 3 min and

every 3 min after that, the increment was increased by 20 W. The exercise tests were terminated when the subjects had reached 85% of the predicted HR_{max}, had failed to maintain the cycling speed, or had presented abnormal signs or symptoms, such as dizziness, near syncope, or an abnormal ECG. After termination of the exercise, the combined effect of sympathetic withdrawal and parasympathetic reactivation was determined by HRR for the first minute after termination.

Throughout the experiment, expired gas samples were collected. The $\dot{V}O_{2\text{ peak}}$ was predicted from the extrapolation to predict HR_{max}. Furthermore, if the subjects had been unable to maintain the cycling speed or had presented abnormal signs or symptoms, such as dizziness, near syncope, or abnormal ECG, the value was used as their individual $\dot{V}O_{2\text{ peak}}$. The autonomic and cardio-respiratory responses to exercise were then evaluated at 3 intensities: low ($< 50\%$ $\dot{V}O_{2\text{ peak}}$), moderate (50–70% $\dot{V}O_{2\text{ peak}}$), and high ($> 70\%$ $\dot{V}O_{2\text{ peak}}$) which had been determined from the graded exercise test. In addition, blood samples were collected before and after the exercise to measure serum sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (HCO_3^-) concentrations by an indirect ion selective electrode (ISE) method and by blood glucose concentration using the Hexokinase method. The laboratory testing was done at the Clinical Chemistry Laboratory of Srinagarind Hospital at Khon Kaen University.

2.4. Daily physical activity and dietary records

Additionally, all subjects were asked to keep physical activity and dietary records for two days of the week and one day on the weekend. Then, the physical activity data was calculated [9], and the dietary intake data was analyzed by the Inmucal-nutrients® Version 3 Software (Thailand).

2.5. HRV

HRV was analyzed for the following 5 periods: (1) 5 min of baseline, (2) during low-intensity exercise, (3) during moderate-intensity exercise, (4) during high-intensity exercise, and (5) at 5-min recovery. The time domain variables included the SDNN, which was used to estimate the overall HRV, and the square root of the mean of the sum of the squares of differences between adjacent normal and normal intervals (RMSSD), which are a reflection of vagal activity. For frequency domain (ms^2), the LF component is the integral over the frequency range of 0.04–0.15 Hz which reflects both sympathetic and vagal activity. The HF component is the integral from 0.15–0.40 Hz and predominantly evaluates vagal activity. LF/HF ratio is calculated to indicate sympathovagal balance [10].

2.6. Statistical analysis

Except where otherwise noted, the data has been expressed as a mean $\pm$ SD. Statistical analysis was performed using the paired t-test for variables within a group (StatMost version 3.6 software, DataMost, USA). Repeated measures analysis of variance was used to compare the differences between the subject groups (the patients and the controls) and the period of each variable (at rest, during exercise, and recovery). A value of $p < 0.05$ was considered to be statistically significant.

Table 1
Anthropometry and body composition of the subjects.

	Control subjects	BrS patients
Age (yr)	47 ± 8	50 ± 6
Height (m)	1.66 ± 0.04	1.69 ± 0.04
Body mass (kg)	68.4 ± 10.4	67.5 ± 9.6
BMI (kg/m^2)	24.7 ± 3.64	23.6 ± 2.48
Lean body mass (kg)	49.9 ± 5.14	48.5 ± 4.00
Body fat (%)	23 ± 9	24 ± 9
Fat mass (kg)	15.4 ± 7.54	16.1 ± 7.88
Waist circumference (cm)	78.0 ± 9.70	78.3 ± 7.30
Hip circumference (cm)	91.8 ± 6.40	91.9 ± 4.08
WHR	0.85 ± 0.06	0.85 ± 0.05

Data are expressed as mean $\pm$ SD; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients without drug prescribe.
BMI=body mass index; WHR=waist to hip circumference ratio.

3. Results

3.1. Demographic and clinical characteristics

The subjects in both groups were overweight (Table 1). There were no significant differences in anthropometry and body composition of the subjects between groups. No subject had taken anti-arrhythmic drugs or any other drug for cardiac diseases.

3.2. Cardio-respiratory measurements

All subjects reached their individual $\dot{V}O_{2\ peak}$ because they had failed to maintain the cycling speed although their HR had not reached 85% of the predicted HR_{max}. During exercise, the resting HR and % $\dot{V}O_{2\ peak}$, and the respiratory exchange ratio (RER) at all intensities were not significantly different between the groups. Also, all of them had a significantly lower % $\dot{V}O_{2\ peak}$ and RER during low-intensity ($p < 0.01$) and moderate-intensity ($p < 0.05$) exercise rather than during high-intensity exercise. During the recovery period, both groups had lower HR than at the end of the exercise, but the values were still higher than their resting values ($p < 0.05$, Table 2).

3.3. HRV

Regarding the controls and BrS patients during exercise at every level of intensity, the SDNN and the LF were lower than the baseline and increased to higher values than the baseline during recovery ($p < 0.05$, Figs. 1 and 3) without any significant difference between groups and intensities. RMSSD in the controls were lower than the baseline during exercise and recovery ($p < 0.05$, Fig. 2) while in the BrS patients were not different between any time point. There was no significant difference in RMSSD between groups and intensities. During exercise, both groups showed a lower HF than the baseline ($p < 0.05$, Fig. 4). During recovery, the
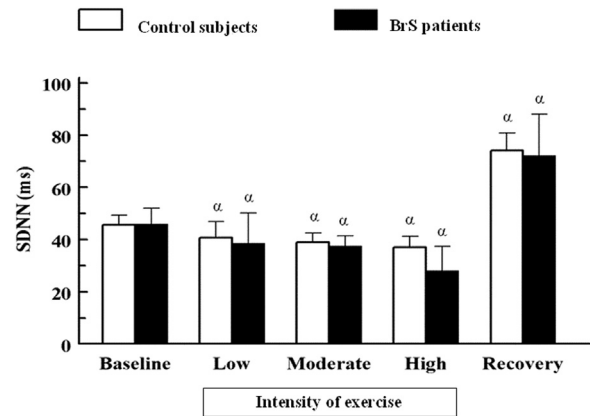

Fig. 1. Standard deviation of all normal to normal intervals (SDNN (ms)) at baseline, exercise and recovery period. Values are mean $\pm$ SE; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients. $^{\alpha}$Significantly different from baseline period within the group ($p < 0.05$).
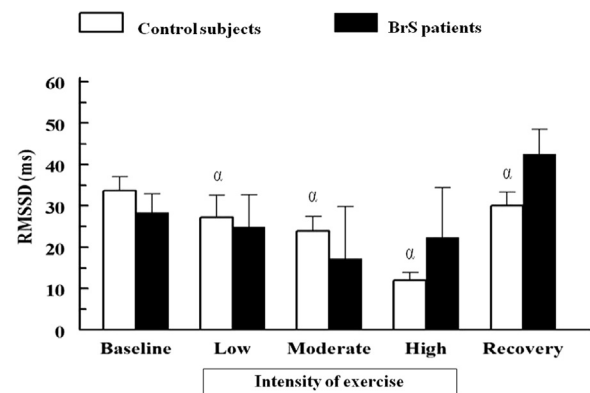

Fig. 2. The square root of the mean of the sum of the squares of differences between adjacent normal to normal intervals (RMSSD (ms)) at the baseline, exercise, and recovery periods. Values are mean $\pm$ SE; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients. $^{\alpha}$Significantly different from baseline period within the group ($p < 0.05$).

controls still showed a lower HF but the BrS patients showed a higher HF than the baseline ($p < 0.05$, Fig. 4). In addition, the controls exhibited a decreased LF/HF at low-intensity exercise and an increased LF/HF at higher-intensity exercise and recovery than the baseline ($p < 0.05$, Fig. 5). The BrS patients seem to show decreased LF/HF during exercise and recovery than the baseline but did not reach statistical difference. However, they had a lower LF/HF during recovery than the controls ($p < 0.05$, Fig. 5). In both groups, there were no significant differences in all HRV parameters between intensity.

Table 2
Blood chemistry parameters before and immediately after the exercise.

	Glucose (mmol/L)	Na$^+$ (mmol/L)	K$^+$ (mmol/L)	Cl$^-$ (mmol/L)	HCO$_3^-$ (mmol/L)
Controls subjects					
Before	4.94 ± 0.49	139.5 ± 2.85	4.50 ± 0.50	102.0 ± 2.39	29.0 ± 2.41
After	4.96 ± 0.39	139.3 ± 2.24	4.37 ± 0.34	102.2 ± 2.20	27.5 ± 2.87
BrS patients					
Before	4.85 ± 0.36	138.4 ± 2.01	5.15 ± 0.79*	102.1 ± 2.17	28.7 ± 3.67
After	4.82 ± 0.50	138.6 ± 2.06	4.91 ± 0.71*	102.1 ± 1.97	28.3 ± 2.67

Data are expressed as mean $\pm$ SD; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients without drug prescribe.
Na$^+$=sodium; K$^+$=potassium; Cl$^-$=chloride; HCO$_3^-$=bicarbonate.
* Significantly different from the control subjects ($p < 0.05$).

Fig. 3. Low frequency component (LF(ms^2)) at baseline, exercise, and recovery periods. Values are mean $\pm$ SE; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients. $^\alpha$Significantly different from baseline period within the group ($p < 0.05$).
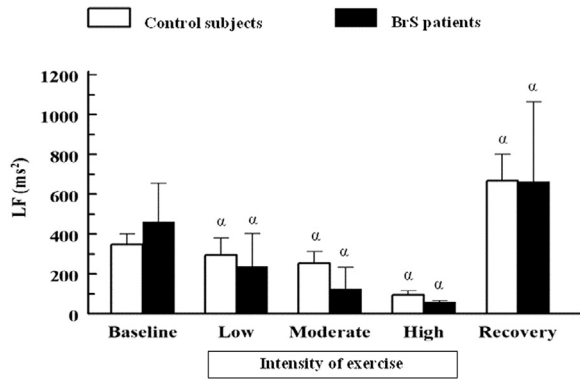

Fig. 4. High frequency component (HF(ms^2)) at baseline, exercise, and recovery periods. Values are mean $\pm$ SE; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients. $^\alpha$Significantly different from baseline period within the group ($p < 0.05$).

Fig. 5. Ratio of low to high frequency component (LF/HF ratio) at baseline, exercise, and recovery periods. Values are mean $\pm$ SE; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients. $^\alpha$ Significantly d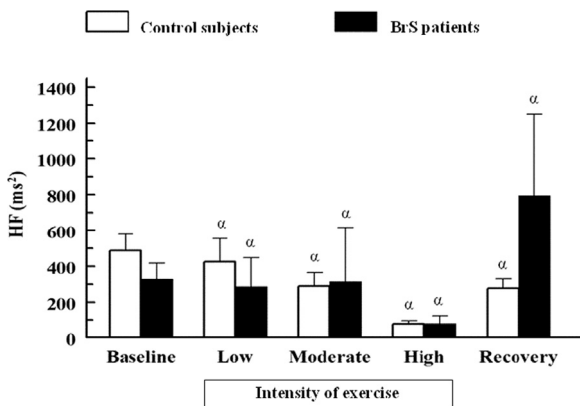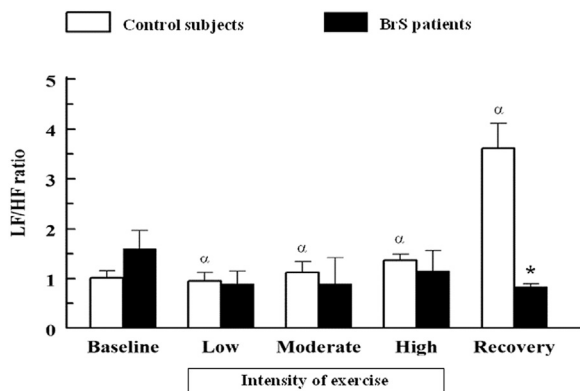ifferent from baseline period within the group ($p < 0.05$). *Significantly different between groups at the same period ($p < 0.05$).

3.4. Blood parameters

All patients had greater resting serum K$^+$ concentrations before and after the exercise when compared to the controls ($p < 0.05$, Table 3). However, they did not have any significant differences in other parameters when compared to the controls (Table 3).

Table 3
Physiological characteristics before and responses to exercise.

	Control subjects	BrS patients
HR$_{before}$ (min^{-1})	63 $\pm$ 7	60 $\pm$ 7
HR$_{peak}$ (min^{-1})	118 $\pm$ 17	101 $\pm$ 14*
HR$_{after}$ (min^{-1})	76 $\pm$ 10	69 $\pm$ 9*
HRR (beats)	28 $\pm$ 8	22 $\pm$ 8*
$\dot{V}O_{2\ peak}$ (ml/kg/min)	22 $\pm$ 7	16 $\pm$ 4*
Maximum exercise work load		
W	83 $\pm$ 20	65 $\pm$ 18*
W/kg	1.24 $\pm$ 0.34	0.95 $\pm$ 0.26*
% $\dot{V}O_{2\ peak}$		
Low intensity-exercise	41 $\pm$ 8$^{\#\#}$	44 $\pm$ 6$^{\#\#}$
Moderate intensity-exercise	61 $\pm$ 6$^{\#}$	59 $\pm$ 7$^{\#}$
High intensity-exercise	91 $\pm$ 12	93 $\pm$ 11
RER		
Low intensity-exercise	0.78 $\pm$ 0.07$^{\#\#}$	0.80 $\pm$ 0.07$^{\#}$
Moderate intensity-exercise	0.82 $\pm$ 0.07$^{\#\#}$	0.84 $\pm$ 0.07$^{\#}$
High intensity-exercise	0.91 $\pm$ 0.08	0.92 $\pm$ 0.07

Data are expressed as mean $\pm$ SD; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients without drug prescribe.
HR before the=heart rate before the exercise; %HR$_{max}$=percent of maximum heart rate; HRR=heart rate recovery (defined as decay of heart rate from peak exercise to one minute after the exercise termination); HR$_{after}$=heart rate immediately after the exercise during recovery period; $\dot{V}O_{2\ peak}$=peak oxygen consumption.

* Significantly different from the control subjects ($p < 0.05$).
# significantly different from high intensity-exercise ($p < 0.05$).
significantly different from high intensity-exercise ($p < 0.1$).

3.5. ECG and ST-segment amplitude

In both groups, the ECG (Fig. 6) and ST-segment amplitude (Table 4) at rest before exercise, during the exercise termination and recovery period were within normal values. ST-segment amplitudes during the last minute of exercise termination were higher than at the last minute of the recovery period in both groups without any difference between groups (Table 4).

3.6. Daily energy intake and energy expenditure

The daily macronutrient and K$^+$ intake did not show any significant difference between the groups. For the BrS patients, the percentage of carbohydrate (CHO), fat, and protein were 76 $\pm$ 3%, 7 $\pm$ 2%, and 17 $\pm$ 2%, respectively, and for the controls, 73 $\pm$ 2%, 9 $\pm$ 1%, and 18 $\pm$ 1%, respectively. The (mean $\pm$ SD) K$^+$ intake of the BrS patients and the controls were 1765 $\pm$ 427 and 1472 $\pm$ 375 mg/day. The total energy expenditure of the BrS patients and the controls were 2453 $\pm$ 337 and 2294 $\pm$ 198 (kcal/day) without any significant difference between the groups.

4. Discussion

The novel findings from this study were that Thai male BrS patients had a more rapid rate of restoration of the parasympathetic and smaller sympathetic activation during the recovery period than the controls. In addition, they had a lower level of cardio-respiratory fitness than their healthy counterparts.

This study has provided preliminary knowledge to further explore the autonomic and the cardio-respiratory responses to exercise in the BrS patients. This knowledge can now be applied to further diagnosis and evaluation and to administer appropriate treatments. However, there may be a question regarding the intensity of exercise and whether or not it was accurate. This is because of concerns regarding whether the $\dot{V}O_{2\ peak}$ was actually
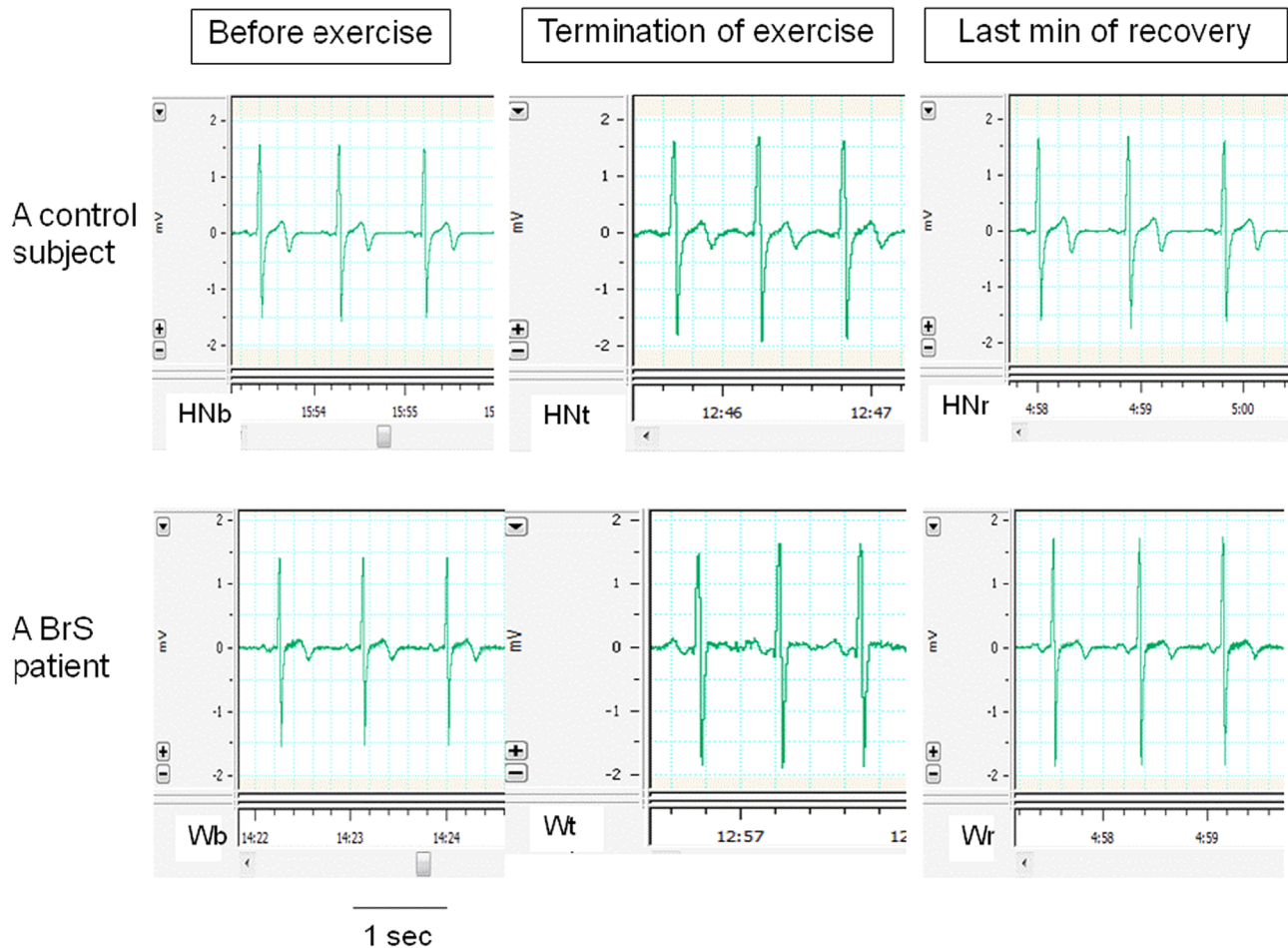
Fig. 6. Responses of electrocardiogram before and termination of exercise and last minute of recovery period in a control subject and a Brugada Syndrome patient without drug prescribe. The standard calibration used was (25 mm/s and 10 mm/mV).

Table 4
ST-segment amplitude after exercise termination for 1 and 5 min.

	Recovery period	
	1 min	5 min
Control subjects	0.07 ± 0.03	0.03 ± 0.02
BrS patients	0.07 ± 0.03	0.05 ± 0.02

Data are expressed as mean $\pm$ SD; $n=23$ control subjects, 11 Brugada Syndrome (BrS) patients without drug prescribe.

achieved. This makes it difficult to evaluate exercise capacity and ANS response during exercise. In fact, the intensity of exercise shown by the percentage of the $\dot{V}O_{2 \text{ peak}}$ and the RER between groups was not significantly different at the same intensities. Therefore, the exercise capacity and ANS response to exercise in this study should be sufficiently accurate to provide a reliable interpretation.

It is noted that in this study BrS patients had an abnormality of plasma K^+ concentration which has been suggested to be a potential trigger of Brugada Syndrome episodes [11]. In the absence of renal dysfunction, the hyperkalemia may result from an abnormal phenotype in BrS characterized by mutation of potassium channels with increasing outward potassium currents (*KCNE3*, *KCND3* and *KCNJ8*) [12–15]. A further molecular study in the patients in this study should be done to confirm this mechanism.

Importantly, it is worth noting that in this study all subjects performed a graded exercise test which was vigorous exercise lasting a few minutes. With increases in plasma catecholamines and K^+ concentrations, exercising at this intensity can be a potential problem even in healthy individuals. Within first few minutes after starting exercise, plasma K^+ concentration increases [16] due to release from contracting skeletal muscles [17]. Furthermore, plasma pH can decrease by 0.4 units [18], and catecholamines can increase up to 15 fold (as high as 0.5–1 μM at the level of the single ventricular myocyte) [19,20]. During exercise in healthy individuals, there is K^+ uptake in non-contracting tissues which prevents an excessive increase in plasma K^+ concentration [21–22], which reduces the overall increase in K^+ concentrations. During exercise recovery, there is a transient hypokalemia [16] resulting from an increment in the skeletal muscle Na^+–K^+ ATPase activity which is stimulated via beta-2 adrenoceptors promoting K^+ uptake [20]. During recovery there is also reported to be a marked vagal rebound [20]. The period of post-exercise hypokalemia may last 90 min or longer depending upon the intensity of the exercise [23]. The reduction in hyperkalemia during the recovery period may be a beneficial effect of exercise in the BrS patients in this study. However, a disruption of this normal protective mechanism may cause SCD in BrS patients. This has been confirmed by previous studies suggesting that the increased vagal tone and/or the decreased sympathetic activity, together with ionic imbalance were important mechanisms in the arrhythmogenesis of BrS [24,25]. The reduction of nor-epinephrine in BrS could lead to an impaired stimulation of β-adrenoceptors. It

could contribute to the reduction of cAMP and alter the subsequent signaling pathway having potential implications for arrhythmogenesis [24] and subsequent myocardial infarction [25]. In this study, sympathovagal and ionic imbalances during recovery after the exercise test were also found. In fact, a recent study reviewed the role of exercise stress testing in BrS [26]. It was found that an exercise test can worsen the ST abnormalities in BrS patients and can produce ventricular arrhythmias. The author suggested that BrS patients should not perform vigorous exercise. It is noted that we did not monitor the right precordial leads (V_1 to V_3) in which ST-segment elevation is important in identifying Brugada Syndrome. However, although we could not monitor Brugada-type ECG during the experiments, the post-experiment analysis of the recording made by the implanted cardioverter-defibrillators showed no Brugada ECG throughout the experiments. We measured ECG during the experiments with modified chest lead V4 (MCL4) [8] because we wished to investigate HRV in these patients and the measurement of HRV is most effectively done with a large R wave because it provides a more accurate determination of RR interval. Together with mild resting pre-exercise hyperkalemia this may imply that the patients in this study were not in a severe condition and had a good prognosis [27]. Nonetheless, a further research on BrS patients is needed to explore the ECG a few days after the exercise test. Moreover, it is unclear whether there are different responses to low- intensity and moderate-intensity exercise in BrS patients compared to controls. Thus, further research is needed to investigate the sympathovagal and cardio-respiratory changes after low-intensity and moderate-intensity exercise in order to provide further information as to whether the BrS patients may gain benefit from exercise training at one or more intensities.

In addition, evidence of similar resting HR's before exercise in the patients and in the controls implies similar autonomic activity at rest during the daytime in both groups of subjects. In contrast, previous studies have reported changes in the nocturnal HR of BrS patients [3,28]. The discrepancy of the results may be due to the fact that this study was conducted during the daytime. The abnormal HR in the patients mostly occurs at night [28]. Therefore, differences in resting HR were not shown during the daytime. The other explanation might be related to the severity of the disease in the studied population. The patients in this study were survivors of cardiac arrest who had had an ICD inserted for secondary prevention. Moreover, they were regularly being seen for ICD checkups at the Queen Sirikit Heart Center of the Northeast, Thailand. The patients in the earlier study had been hospitalized after sudden cardiac arrest for further management. Therefore, the stage of the syndrome may have been different [3]. With respect to this study, an important note, that should be emphasized, is that the ICD implanted in the patients does not control cardiac rhythm. It just stimulates cardiac contraction when there is cardiac arrest. Therefore, the patients in this study had physiological control of the HR. Moreover, there may be a question about the resting HR, which is similar to the controls, although they had been taking anti-arrhythmic drugs. This may be due to the low dose of drugs (e.g., β-blocker for our BrS patients which was 6.25 mg carvedilol twice a day).

It was surprising that the BrS patients had achieved a smaller HRR than the controls, because they had had a larger increase in vagal activity and a withdrawal of sympathetic activity, which should have increased HRR after the termination of the exercise. This may be due to the patients' lower peak exercise workload which may have resulted in a lower peak HR than the controls. When the HRR was considered as a proportion of the increase in HR from resting to the maximum level at the termination of exercise and was not different between groups, this was confirmed. In fact, HRR in the BRS patients is still controversial since it

was shown to be similar to [29], higher than [30], or lower than [30] the controls. This may be attributed to the electrophysiologic characteristics [30] of the patients.

Patients in this study reached their individual $\dot{V}O_{2\ peak}$ because they could not maintain the cycling speed although their HR did not reach 85% of the predicted HR_{max}. The low $\dot{V}O_{2\ peak}$ in the controls may be explained by the fact that these subjects were very unfit patients and controls who had not been habitual exercisers and who had been unable to exercise at a higher intensity. Middle-aged South Asian individuals have been shown to have lower $\dot{V}O_{2\ peak}$ than their European counterparts [31]. Moreover, the healthy subjects in this study had similar $\dot{V}O_{2\ peak}$ (22 ± 2 ml/kg/min) to Thai subjects of the same age as had been reported in a previous study (25.9 ± 3.4 ml/kg/min) [32]. In this study BrS patients had lower $\dot{V}O_{2\ peak}$ than the controls. Regarding the inverse relationship between cardio-respiratory fitness and heart failure [7], the impaired cardio-respiratory fitness may be due to imbalanced cardiac sympathovagal and a reduction in K^+ concentration induced by the exercise test.

5. Conclusions

We suggest that Thai BrS patients had a more rapid rate of restoration of the parasympathetic and smaller level of sympathetic activation during recovery after the graded exercise. This imbalanced cardiac sympathovagal may contribute to impaired cardio-respiratory fitness. They exhibited hyperkalemia which was reduced according to the exercise. Further work is needed to assess the possible contribution of such autonomic differences to the cardiac pathophysiology of BrS patients.

Conflict of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.joa.2015.09.001.

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