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Original Article

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

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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

Abbreviations: BrS, total Brugada Syndrome; BrS-D, patients who took anti-arrhythmic drugs; BrS-ND, patients who did not take anti-arrhythmic drugs; SCD, sudden cardiac death; K^+, potassium; ANS, autonomic nervous system; ICD, implantable cardioverter-defibrillator; $O_{2\ peak}$, peak oxygen consumption; ECG, electrocardiogram; RER, respiratory exchange ratio; HR, heart rate; HRV, heart rate variability; HRR, heart rate recovery; VF, ventricular fibrillation; VT, ventricular tachycardia; SDNN, standard deviation of all normal sinus RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent normal to normal intervals; LF, low frequency; HF, high frequency; CHO, carbohydrate.

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ANS activity responses related to exercise has not been previously investigated. In addition, cardio-respiratory fitness, determined by peak oxygen consumption ($\dot{V}O_{2\ peak}$), was reported to be strongly and inversely related to heart failure [7]. Therefore, $\dot{V}O_{2\ peak}$ may reveal different levels of cardio-respiratory fitness in patients with Brugada Syndrome. However, until now, no research investigating $\dot{V}O_{2\ peak}$ 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 $\dot{V}O_{2\ peak}$ 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 $\dot{V}O_{2\ peak}$. The autonomic and cardio-respiratory responses to exercise were then evaluated at 3 intensities: low ($<50\%$ $\dot{V}O_{2\ peak}$), moderate (50–70% $\dot{V}O_{2\ peak}$), and high ($>$ 70% $\dot{V}O_{2\ peak}$) 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 ± 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.