European Review for Medical and Pharmacological Sciences 2018; 22: 1102-1105

Heart rate variability in children with myocarditis presenting with ventricular arrhythmias

N. LING, C.-L. LI, Z.-Z. WANG, H.-N. ZHANG, H. XU, X.-J. AN

Department of Cardiology, Xuzhou Children's Hospital, Xuzhou, Jiangsu, China

Abstract. – OBJECTIVE: We aimed to investigate the heart rate variability in children with myocarditis presenting with ventricular arrhythmias.

PATIENTS AND METHODS: The study compared the characteristics of heart rate variability (HRV) among 67 children with viral myocarditis (VMC), presenting with (n=35) and without (n=32) ventricular arrhythmias and a control group of 30 healthy children.

RESULTS: Compared with the control group, the HRV time-domain indicators of children with VMC were significantly lower ($p<0.05$); also, the indicators of children with ventricular arrhythmias were significantly lower than those of children without ventricular arrhythmias ($p<0.05$). Equally, during both the lucid and sleep periods, the time-domain indicators of HRV were significantly lower in patients with VMC and arrhythmias than in either the control group ($p<0.05$) or the group with VMC but no ventricular arrhythmias ($p<0.05$).

CONCLUSIONS: We conclude that the HRV of children with VMC probably decreased because of impaired vagal nerve function, with ventricular arrhythmias developing only when the decrease was most significant. Thus, HRV can be a useful predictive indicator for ventricular arrhythmias in children with VMC.

Key Words:
Viral myocarditis, Ventricular arrhythmias, Heart rate variability.

Introduction

Viral myocarditis (VMC), which has an incidence of 0.5%-2.6%, is typically caused by Coxsackievirus B or other enteroviruses that cause focal or diffuse myocardial lesions[1]. Although VMC is curable, children may have *arrhythmic sequelae*, including tachycardia and abnormalities of atrial or ventricular rhythm[2]. Unfortunately, the mortality associated with acute fulminant VMC can be high as a consequence, with multiple organ failure and malignant ventricular arrhythmia being the major causes of death[3]. However, there is an immediate correlation between imbalances of the autonomic nerve system and the occurrence of ventricular arrhythmias[4]. Heart rate variability (HRV) is a non-invasive, highly sensitive assessment that is frequently used as a quantitative indicator of autonomic nervous function in the diagnosis, treatment, and prognosis of related disease[5]. In this investigation, we analyzed the HRV results of children with VMC and ventricular arrhythmias, with the aim that these results might provide indicative reference values for clinical treatment.

Patients and Methods

Study Design and Participants

We enrolled 67 consecutive patients admitted to Xuzhou Children's Hospital with a diagnosis of VMC between January 2014 and January 2016. We divided them into an arrhythmia group (35 cases) and a non-arrhythmia group (32 cases). The research team obtained the approval of the Ethics Committee of Xuzhou Children's Hospital and informed consents of the children patients' guardians VMC was diagnosed according to the VMC diagnostic criteria of the National Cardiovascular Sessions[6]. The inclusion criteria were as follows: a) age 4-12 years; b) VMC diagnosed according to the VMC diagnostic criteria; c) onset of VMC within 1 month of admission. The exclusion criteria were as follows: a) patients with cardiac disease, including congenital heart diseases or primary arrhythmias; b) patients with metabolic disease, such as thyroid gland dysfunction; c) patients with poor compliance; d) patients for whom there was incomplete clinical data. Once informed consent had been obtained from parents, we divided the participants into an arrhythmia group and a non-arrhythmia group. Children in the arrhythmia group were required to be symptomatic and presenting with premature ventricular contraction, ventricular tachycardia, or ventricular fibrillation. As a control group, we randomly enrolled 30 healthy children during the same period.

Corresponding Author: Xinjiang An, MD; e-mail: anxinjian001@163.com

Protocol and Outcomes

We used a DCG (Dynamic Electrocardiography) Monitoring System (Century Series 3000, Biomedical System Corporation, New York, NY, USA) to monitor children in all three groups. No child was administered any drug known to affect the electrophysiological properties of the heart for 1 week before monitoring. We then used several time-domain indicators of HRV for further analysis: a) SDNN (standard deviation of NN intervals), the standard deviation of consecutive regular R-R intervals in 24 h; b) SDANN, the standard deviation of the average of 5-min R-R intervals in 24 h; c) the SDNN index, the average standard deviation of the 5-min R-R intervals in 24 h; d) RMSSD, the root mean square of successive heartbeat interval differences in 24 h; e) PNN50, the percentage of consecutive R-R intervals differing by more than 50 ms. Monitoring was for 24 h, from 08:00 am to 9:00 pm set as the lucid period and from 9:00 pm to 06:00 am set as the sleep period.

Statistical Analysis

Data analysis was performed using IBM SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). All quantitative data are presented as mean ± standard deviation, and enumeration data are presented as percentages. Statistical differences were analyzed by one-way analysis of variance, and differences between the two groups were analyzed by the Least-Significant Difference test. Enumeration data were compared between groups using the χ^2 test. Differences of $p<0.05$ were considered statistically significant.

Results

Participants

We enrolled 67 consecutive patients diagnosed with VMC and divided them into an arrhythmia group (35 cases) and a non-arrhythmia group (32 cases). In the arrhythmia group, there were 20 boys and 15 girls, and the average age was 7.6 ± 2.5 years; in the non-arrhythmia group, there were 18 boys and 14 girls, and the average age was 7.7 ± 2.6 years. We also enrolled 30 healthy children in the control group, of which 17 were boys, 13 were girls, and the average age was 7.6 ± 2.7 years. There were no statistically significant differences in sex or age among the three groups ($p>0.05$).

Comparison of HRV Time-Domain Indicators Among the Three Groups

Compared with the control group, the HRV time-domain indicators of children with VMC were significantly lower ($p<0.05$); also, the indicators of children with ventricular arrhythmias were significantly lower than those of children with no ventricular arrhythmias ($p<0.05$). See Table I.

Comparison of Time-Domain Indicators During the Lucid and Sleep Periods

Compared with the control group, the HRV time-domain indicators in the VMC group were significantly lower during both the lucid and sleep periods ($p<0.05$); also, the HRV indicators of children with arrhythmias were significantly lower than those of children with no arrhythmias during both periods ($p<0.05$). See Tables II and III.

Discussion

The etiology of VMC is multifactorial, related to the presence of viral infection, the genetic background of the host, the immunoreaction in the host, and the oxidation reaction in the host[6]. As a severe complication of myocarditis, ventricular arrhythmias can persist through childhood into adulthood and may be associated with dilated cardiomyopathy as the disease passes through different stages[7]. Arrhythmia is the external manifestation of irregular electrical transmission caused by an abnormality in the structure and function of the conducting system of the heart[8]. Thus, myocarditis could lead to not only lesions of the myocardium and matrix, but also dysfunction of the cardiac pacing and conduction systems[9]. The natural history of myocarditis involves myocardial

Table I. Comparison of the time-domain indicators in all groups($\bar{x} \pm s$).

Group	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	RMSSD (ms)	PNN50 (%)
Control	141.27 ± 28.15	121.36 ± 23.47	53.28 ± 11.41	55.85 ± 14.77	21.43 ± 7.03
Non-arrhythmia	103.28 ± 19.75*	84.69 ± 17.98*	42.63 ± 9.82*	39.07 ± 12.63*	9.85 ± 3.11*
Arrhythmia	68.32 ± 15.84*#	65.40 ± 16.73*#	30.17 ± 9.95*#	28.75 ± 9.01*#	5.85 ± 1.70*#

Note: *refers to the significant difference between the value and the control group ($p<0.05$); #refers to the significant difference between the value and non-arrhythmias group ($p<0.05$).

Table II. Comparison of time-domain indicators among all groups during the lucid period ($\bar{x} \pm s$).

Group	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	RMSSD (ms)	PNN50 (%)
Control	105.24 ± 23.86	104.58 ± 18.67	39.18 ± 9.42	38.57 ± 12.06	11.22 ± 3.64
Non-arrhythmia	86.27 ± 20.33*	73.82 ± 16.40*	35.75 ± 7.22*	26.46 ± 8.51*	7.54 ± 2.01*
Arrhythmia	60.43 ± 16.95*#	57.28 ± 17.36*#	20.65 ± 5.17*#	15.33 ± 4.88*#	3.10 ± 1.00*#

Note: *refers to the significant difference between the value and the control group ($p<0.05$); #refers to the significant difference between the value and non-arrhythmias group ($p<0.05$).

Table III. Comparison of time-domain indicators among all groups during the sleep period ($\bar{x} \pm s$).

Group	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	RMSSD (ms)	PNN50 (%)
Control	162.74 ± 30.94	133.67 ± 26.66	65.57 ± 14.31	76.92 ± 15.04	42.75 ± 12.43
Non-arrhythmia	114.65 ± 28.72*	90.52 ± 20.19*	49.52 ± 11.77*	40.12 ± 14.66*	15.22 ± 4.13*
Arrhythmia	79.22 ± 20.14*#	72.85 ± 15.83*#	38.67 ± 10.64*#	31.63 ± 11.16*#	8.61 ± 2.35*#

Note: *refers to the significant difference between the value and the control group ($p<0.05$); #refers to the significant difference between the value and non-arrhythmias group ($p<0.05$).

ischemia, anoxia, and inflammatory factors that manifest as increased heart rate and decreased HRV[10]. The heart is dominated by sympathetic and vagal nerve activity[11]. When the sympathetic nerves are stimulated, the activation of norepinephrine receptors on the myocardial cell membrane are accelerated, resulting in an increase in heart rate and myocardial contractility. By contrast, the action of acetylcholine from cardiac vagal nerves on the myocardial cell membrane can decrease both the heart rate and myocardial contractility. Under normal physiological conditions, acetylcholine and norepinephrine can suppress each other, but the effect of the vagal nerve outweighs that of the sympathetic nerve[12]. Indeed, despite the fact that sinoatrial node activity is under both sympathetic and vagal control, the quantity of vagal nerve inside the sinoatrial node is greater than that of the sympathetic nerve, so cells of the sinoatrial node are more sensitive to vagal nerve input. Therefore, the heart beat rhythm is mainly controlled by the vagal nerve, with the sympathetic nerve exerting an auxiliary effect[13]. Changes in autonomic nerve activity could be reflected by variations in the R-R intervals. The methods applied to detect HRV include time and frequency-domain analyses, with the 24-h time-domain analysis being stable and repeatable, making it the most frequently used method when evaluating HRV[14]. The SDNN can reflect the overall state of HRV and can help evaluate the overall tension of the autonomic nerve[15]. Meanwhile, SDANN and the SDNN index can reflect gradual changes in heart rate, thereby serving as sensitive indicators for the evaluation of sympathetic nerve function. Thus, as there is an increase in sympathetic nerve tension, SDANN and the SDNN index decrease significantly[16]. By contrast, RMSSD can help assess faster switches in the heart rate, serving as a major indicator in the evaluation of vagal nerve function, where it decreases significantly with any decrease in vagal nerve tension[17]. In this study, we found that the HRV time-domain indicators in patients with VMC were significantly lower compared with those in the control group. Also, the indicators were significantly lower in the children with than in those without ventricular arrhythmias. During the lucid and sleep periods, the HRV time-domain indicators of patients with VMC were also significantly lower than those of the control group, and the indicators of patients with ventricular arrhythmias were significantly lower than for those with no ventricular arrhythmias. These findings indicate that there are major changes in autonomic nerve function (predominantly impaired vagal nerve function) in children with VMC; however, at present, the precise mechanism of HRV decrease in these children remains unclear. Nikitina et al[18] found that changes in β-receptor function may occur at any stage of myocarditis and that a significant increase in β-adrenoreceptor sensitivity might be induced by the augmentation of stimulatory G-protein concentrations after myocarditis. However, Li et al[19] argued that impairment of cardiac muscle caused by myocarditis might cause lesions of inhibitory receptors on the sympathetic nerve, triggering excessive enhancement of sympathetic nerve activity and inhibition of vagal nerve activity, leading to a decrease in HRV. Children with VMC and

arrhythmias may, therefore, suffer impairment of the cardiac autonomic nerves that is more severe than in those without arrhythmias. Indeed, the electrical stability of the myocardium is mainly dependent on the balance between vagal and sympathetic nerve activities, which in turn affect HRV and can be used to evaluate the severity of ventricular arrhythmias. If vagal nerve activity increases, HRV will increase and protect against ventricular fibrillation, but if sympathetic nerve activity increases, HRV will decrease and may lead to the development of malignant arrhythmias. Circadian changes in HRV could also indicate variations in autonomic nerve function with high-sensitivity[20]. Circadian HRV usually decreases in children with myocarditis, particularly in those with ventricular arrhythmias.

Conclusions

Vagal nerve functions are probably impaired in children with myocarditis, leading to decreased HRV, and this appears most markedly in children with ventricular arrhythmias. Therefore, HRV could be used as a predictive indicator for the development of ventricular arrhythmias in children with VMC.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Zhai X, Bai B, Yu B, Wang T, Wang H, Wang Y, Li H, Tong L, Wang Y, Zhang F, Zhao W, Zhong Z. Coxsackievirus B3 induces autophagic response in cardiac myocytes in vivo. Biochemistry (Mosc) 2015; 80: 1001-1009.
2) Baksi AJ, Kanaganayagam GS, Prasad SK. Arrhythmias in viral myocarditis and pericarditis. Card Electrophysiol Clin 2015; 7: 269-281.
3) Chu PL, Chang WT, Chen WJ, Chen YS. Acute viral myocarditis presenting as sudden cardiac arrest and refractory ventricular tachycardia. Am J Emerg Med 2004; 22: 628-629.
4) Gao X, Peng L, Zeng Q, Wu ZK. Autonomic nervous function and arrhythmias in patients with acute viral myocarditis during a 6-month follow-up period. Cardiology 2009; 113: 66-71.
5) Cheng Z, Li-Sha G, Yue-Chun L. Autonomic nervous system in viral myocarditis: Pathophysiology and therapy. Curr Pharm Des 2016; 22: 485-498.
6) Frishman WH, Zeidner J, Naseer N. Diagnosis and management of viral myocarditis. Curr Treat Options Cardiovasc Med 2007; 9: 450-464.
7) Lu YF, Zhang QY, Wang LH, Liu XY and Zhang SX. The protective effects of taurine on experimental autoimmune myocarditis. Eur Rev Med Pharmacol Sci 2017: 21: 1868-1875.
8) Huttin O, Frikha Z, Brembilla-Perrot B, Sellal JM, Mandry D, Aliot E, Juilliere Y, Sadoul N, Selton-Suty C. Acute myocarditis presenting with ventricular arrhythmias: the role of CMR in the differential diagnosis of ARVD. Intern Med 2013; 52: 1915-1918.
9) Yasukawa H, Oba T, Fukumoto Y. Alterations in coxsackievirus and adenovirus receptor confer susceptibility to ventricular arrhythmia with an ischemic event. J Am Coll Cardiol 2014; 63: 560-562.
10) Steinke K, Sachse F, Ettischer N, Strutz-Seebohm N, Henrion U, Rohrbeck M, Klosowski R, Wolters D, Brunner S, Franz WM, Pott L, Munoz C, Kandolf R, Schulze-Bahr E, Lang F, Klingel K, Seebohm G. Coxsackievirus B3 modulates cardiac ion channels. FASEB J 2013; 27: 4108-4121.
11) Li-Sha G, Jing-Lin Z, Li L, Guang-Yi C, Xiao-Wei L, Yue-Chun L. Nicotine inhibits the production of proinflammatory cytokines of mice infected with coxsackievirus B3. Life Sci 2016; 148: 9-16.
12) Lu SC, Zhang JP, Zhu YP, Zhou YN, Xiao N, Guo XC, Wang XL, Rong J, Wu MF. A randomized clinical study on optimum proposal of integration of disease and syndrome to treat viral myocarditis. Chin J Integr Med 2015; 21: 176-182.
13) Niu L, An XJ, Tian J, Wang Y. 124 cases of clinical analysis of children with viral myocarditis. Eur Rev Med Pharmacol Sci 2015; 19: 2856-2859.
14) Pizzi C, Manzoli L, Mancini S, Costa GM. Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. Eur Heart J 2008; 29: 1110-1117.
15) Morozova MP, Lukoshkova EV, Gavrilova SA. Some aspects of heart rate variability estimation in rats. Ross Fiziol Zh Im I M Sechenova 2015; 101: 291-307.
16) Ichikawa R, Sumitomo N, Komori A, Abe Y, Nakamura T, Fukuhara J, Matsumura M, Miyashita M, Kanamaru H, Ayusawa M, Mugishima H. The follow-up evaluation of electrocardiogram and arrhythmias in children with fulminant myocarditis. Circ J 2011; 75: 932-938.
17) Langley P, Macgowan GA, Murray A. Circadian variation of human ventricular fibrillation dominant frequency. Resuscitation 2010; 81: 950-955.
18) Nikitina T, Bekbosynova MS, Golitsyn SP, Novikova DS, Loladze NV, Tonevitskii AG. Spectral parameters of heart rate variability and frequency of detection of autoantibodies to beta(1)-adrenoreceptors in patients with tachyarrhythmias: idiopathic and at the background of primary myocardial diseases. Kardiologiia 2006; 46: 13-19.
19) Li H, Yang TD. Vagus nerve stimulation may be used in the therapy of myocarditis. Med Hypotheses 2009; 73: 725-727.
20) Cui S, Chen XL, Jiang MX. Study on pathological rhythm of traditional Chinese medicine about circadian distribution of premature ventricular contractions in 240 patients with viral myocarditis. Zhong Xi Yi Jie He Xue Bao 2005; 3: 355-358.