

Assessment of Cardiac Autonomic Function by Using Heart Rate Turbulence in Behcet's Disease

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Abstract

Behcet's disease (BD) is a chronic inflammatory disorder that can affect many systems in the body. Cardiac involvement increases the risk of cardiovascular mortality and occurs in 1% - 5% of patients with BD. Ventricular arrhythmias are believed to be the cause of this increased risk of cardiovascular mortality and it is also thought to be related with cardiac autonomic dysfunction. Heart rate turbulence (HRT) is a new predictor of cardiac autonomic activity. HRT is an independent and powerful predictor of mortality. In this study, we investigated the cardiac autonomic activity which can be determined by HRT in patients with BD. Forty patients with BD (20 men, mean age: 40 ± 9 years, range: 27 - 55 years) were diagnosed according to the International Study Group Criteria (ISGC) and gender and age matched healthy volunteers (20 men, mean age: 39 ± 8 years, range: 26 - 56 years) were included in this study. All of the participants (patients and controls) underwent 24 hours Holter electrocardiogram. HRT parameters, turbulence onset (TO) and turbulence slope (TS) were calculated with HRT (View Version 0.60-0.1 of Software Program). There were no significant differences in TO and TS values between patients with BD and control subject (TO-BD: 0.014 ± 0.03 , TO-Control: 0.011 ± 0.04 ; TS-BD: 7.88 ± 4.9 , TS-Control: 9.42 ± 6.7 respectively). Although increased cardiovascular mortality rates in BD have been shown in many studies, HRT values—detecting the risk of sudden death—do not seem to be altered in this disease.

Keywords

Behcet's Disease, Heart Rate Turbulence, Sudden Cardiac Death, Cardiac Autonomic Activity

1. Introduction

Behcet's disease (BD) is a chronic disorder characterized by acute exacerbations affecting multi-organ system. It is an inflammatory disorder which can be classified as autoimmune or autoinflammatory disease. Although etiology has not been clarified yet, the most acceptable opinion includes genetic background (Human leukocyte antigen (HLA)-B 51, one of the numerous split antigens of HLA-B 5) and some microorganisms or their antigens such as; herpes simplex virus, streptococci, staphylococci, or *Escherichia* species [1]. The prevalence of BD has been reported as 5.2 per 100,000 population (95% CI 0.64 - 9.84), and although some studies in the literature report higher incidence of BD among women, this issue is contradictory in some other studies [2]. Uveitis, dermal lesions, oral and genital ulcers usually can be encountered along the course of BD [3]. Cardiovascular involvement characterized with endocarditis, myocarditis, pericarditis, intracardiac thrombi, endomyocardial fibrosis, coronary arteritis, myocardial infarction and valve disease may occur rarely [4]-[8].

It is shown that patient with BD has an increased mortality rates compared with normal population. Some of the predictors of mortality associated with BD have been identified. Arterial involvement is one of the predictors increasing mortality in patients with BD. It is well known that sudden death can be seen in this disease [9]-[13]. Ventricular arrhythmias are the most common cause of sudden cardiac death in most of the diseases. Dysfunction of cardiac autonomic activity is one of the causes of ventricular arrhythmias. Autonomic nervous system such as central nervous system may be involved in Behcet's disease [14] [15].

Some of the noninvasive parameters for the prediction of cardiac autonomic function such as heart rate variability (HRV), baroreflex sensitivity (BRS) and heart rate turbulence (HRT) have been identified. All of these tests assess the autonomic and reflex modulations of cardiac functions. Deterioration of HRT is correlated with BRS impairment. HRT deterioration reflects cardiac autonomic dysfunction [16]. HRT expresses ventriculophasic sinus arrhythmia, *i.e.*, the early acceleration and the late deceleration of sinus rhythm after single ventricular premature beat (VPB), and it is considered to reflect autonomic nervous system function. HRT is an independent and powerful predictor of mortality and sudden cardiac death in various cardiac abnormalities [17] [18]. In our knowledge, there has been no previous study about HRT parameters in patients with BD.

In this study, we aimed to evaluate cardiac autonomic function by measuring HRT method which could be responsible for the higher rates of cardiovascular deaths in patients with BD.

2. Method

2.1. Study Population

Forty patients with Behcet's disease (20 men, age: 40 ± 9 years, range: 27 - 55 years) diagnosed according to the International Study Group Criteria—ISGC, and age and gender matched healthy volunteers without known cardiovascular disease (20 men, age: 39 ± 8 years, range: 26 - 56 years) were included in this study. Mean duration time of the disease was 7.7 ± 6.3 years (range: 1 - 18 years). Only patients in remission defined according to the clinical and laboratory data were included in this study. Before the study, all participants of this study were informed of the trial and provided written informed consent.

patients with unstable angina, myocardial infarction, heart failure, hypertension, diabetes mellitus, valvular heart disease, non-sinus rhythm, hyperthyroidism, left ventricular hypertrophy, electrolyte disturbances, and other systemic disorders (e.g. chronic renal failure, hepatic failure), smokers, drug users (especially beta-blockers and/or antiarrhythmic drugs) were excluded from the study. Physical examinations and resting 12-lead electrocardiograms (ECGs) of the participants were normal. Routine biochemical and hematological values including fasting blood glucose, blood urea nitrogen, serum electrolytes, thyroid hormones, and hemoglobin levels were in normal ranges.

2.2. 24-Hour Holter Electrocardiogram and HRT

All participants underwent 24-hour Holter ECG. Holter recordings were analyzed with Reynolds Medical Pathfinder Software Version V8.255 (Hereford, England). Turbulence onset (TO) and turbulence slope (TS) values were calculated with the HRT by View Version 0.60-0.1 Software Program (Munich, Germany). While determining the HRT, abnormal beats and areas of artifact, which were accepted as VPB by the computer, were manually identified and excluded. Measurements of HRT were calculated by the original method which has been performed previously by Schmidt *et al.* [18] as shown in Figure 1. TO, which is a measure of the early sinus

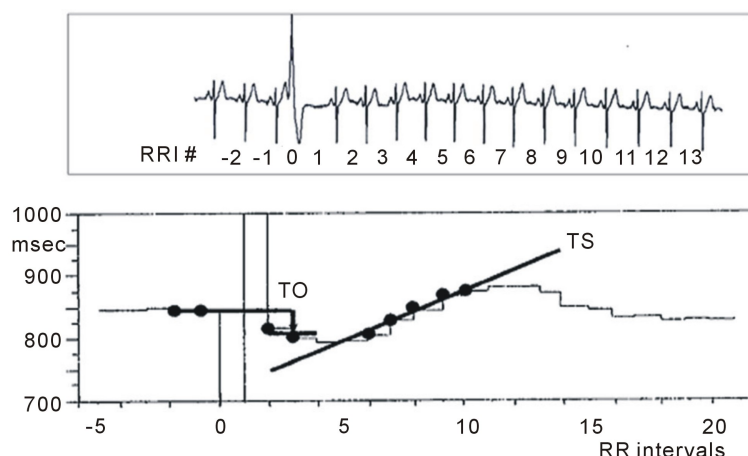


Figure 1. Calculation of heart rate turbulence.

acceleration after a VPB, is expressed as percentage and calculated by following formula:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100$$

where RR_1 and RR_2 are the first and second sinus RR intervals after the VPB, and RR_{-1} and RR_{-2} are the first and second sinus RR intervals preceeding the VPB.

Turbulence slope (TS) is a measure of sinus deceleration rate following the sinus acceleration after a VPB. It is accepted as a maximal positive slope among all slopes of a series of regression lines obtained from all sequences of five consecutive RR intervals (within the first 20 sinus rhythm intervals after a VPB), and expressed as ms/RR. TO was calculated for all VPBs separately and obtained as an average value, whereas TS was calculated based on an average local tachogram.

2.3. Statistical Analysis

Statistical analyses were performed with SPSS for Windows version 11.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as number (%) or the mean \pm SEM (standard error of mean). Comparisons between independent groups were performed by using Student t test. A p value < 0.05 was considered as statistically significant.

3. Results

All patients completed the study. Demographic properties of the patients with behcet's disease and control groups are shown in [Table 1](#). In all participants, rhythm was sinus and none of them had pacemaker. HRT parameters, TO and TS did not differ significantly between the two study groups, as shown in [Table 2](#) (TO-BD: 0.014 ± 0.03 vs TO-Control: 0.011 ± 0.04 ; TS-BD: 7.88 ± 4.96 vs TS-Control: 9.42 ± 6.7 respectively).

4. Discussion

In this present study, the diagnosis of BD has been based on the diagnostic criteria by Japanese and/or International Study Group [19] Behcet's disease leads to some problems in many organ systems. Vascular involvement is seen in 3% - 29% of patients with BD. Vasculitis are observed as venous and/or arterial inflammations. The most encountered vascular lesion is superficial vein thrombosis [20]-[22]. Arterial involvement is less frequent than venous involvement. Carotid, pulmonary, aortic, iliac, femoral and popliteal arteries may also be involved. Less frequently, renal arteries may also be effected [23]. Although acute coronary syndrome due to coronary arterial involvement is a very rare complication, myocardial perfusion defect has been shown with myocardial perfusion scintigraphy in 56% of the patients with BD [24].

Cardiac involvement was 6% in 807 patients with BD [21]. Cardiac lesions were the most frequent arterial involvement in BD and pericarditis was the most frequent cardiac lesion in their study. The other cardiac disorders related with BD were as follows: "endocarditis, intracardiac thrombi, myocardial infarction, endo-

Table 1. Demographic properties of the patients with Behcet's disease and control group.

	Behcet's disease (n: 40)	Control group (n: 40)	
	(Mean \pm SD)	(Mean \pm SD)	p
Age (years)	40.0 \pm 8.9	39.9 \pm 8.4	0.654
Height (cm)	166.9 \pm 8.4	169.4 \pm 8.3	0.996
Weight (kg)	73.8 \pm 13.8	73.6 \pm 11.9	0.299
BMI (kg/m ²)	26.3 \pm 4.0	25.0 \pm 4.9	0.847
Heart rate (beats/min)	75.4 \pm 3.6	74.8 \pm 3.4	0.813
SBP (mmHg)	115.9 \pm 10.6	115.7 \pm 9.8	0.956*
DBP (mmHg)	72.2 \pm 5.7	72.5 \pm 6.7	0.781*
Sex (Male %)	20 (% 50)	20 (% 50)	1.000

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *Mann-Whitney U student-t test.

Table 2. Turbulence onsets and turbulence slopes of two groups.

	Behcet's disease (n: 40)	Control group (n: 40)	
	(Mean \pm SD)	(Mean \pm SD)	p
Turbulence onset	0.014 \pm 0.03	0.011 \pm 0.04	0.141
Turbulence slope	7.879 \pm 4.96	9.420 \pm 6.7	0.247

myocardial fibrosis and myocardial aneurysms" [21]. Each of these cardiac lesions may lead to mortality or morbidity. Saadoun *et al.* were reported [12] that one patient died due to endocarditis.

Cardiovascular involvement sometimes manifest as a sudden cardiac death [25]. Previous studies has shown that, sudden cardiac death in patients with BD was more frequent compared with normal population. One of the causes of increased sudden cardiac death in patients with BD is cardiac autonomic dysfunction [26] [27]. Ventricular arrhythmias are the most frequent cause of sudden death especially in cardiac disease. Patients with BD have also frequent ventricular arrhythmias. Increased QT dispersion and degenerated heart rate variability in BD may be indicators of frequent ventricular arrhythmias [9] [23].

Three major factors contribute to the occurrence of ventricular arrhythmias which lead to the sudden cardiac death. These are arrhythmogenic triggering, arrhythmogenic structure and autonomic tonus variability. While arrhythmogenic triggering originates from ventricular ectopic activity, arrhythmogenic structure derives from the myocardial structure. The third factor is the autonomic tonus variability which is accepted as an impairment of myocardial sympathovagal balance. It is also called cardiac autonomic activity. Since it is difficult to determine cardiac autonomic activity by using only one method, all heart rate variability with baroreflex sensitivity and heart rate turbulence methods should be used to define cardiac autonomic activity [28].

Heart muscle is innervated by autonomic nervous system. Autonomic nervous system consists of afferent and efferent pathways of vagal and sympathetic fibers [29]. Efferent nerves in myocardium may reflect the changes in cardiac autonomic system. Changes in cardiac autonomic system have a crucial role in generation of cardiac arrhythmias and sudden death. increased sympathetic and decreased vagal tonus may be the main cause in generation of arrhythmias [28].

Efferent cardiac autonomic activity is mainly under the control of baroreceptor and BRS, and those are related with the mechanism of cardiac arrhythmias. Heart rate turbulence (HRT) values are highly correlated with spontaneous BRS ratios [28]. It is proven that HRT also predicts mortality and sudden cardiac death in various cardiac situations such as postmyocardial infarction [18] after the coronary artery by-pass grafting surgery [30] and chronic heart failure [31]. HRT also predicts the alterations of cardiac autonomic function in non-cardiac diseases such as diabetes mellitus [32] and hyperthyroidism [33]. HRV is also changed in those diseases [34]-[36]. In most studies, cardiac autonomic activity determined by HRT, BRS and HRV were deteriorated but those may not change together even in the same diseases. For example Bigger *et al.* [37] showed an altered HRV after myocardial infarction but BRS and HRT were normal in the same patient population. Furthermore Ortak *et al.* [38] showed increased indices of HRV but parameters of HRT did not change in the same patients after myocardial infarction. As a result, HRT and HRV indices may indicate a different aspects of autonomic nervous system activity and they could provide valuable prognostic information value.

There are limited numbers of studies related with the cardiac autonomic activity in Behcet's disease. Some of the results of these studies are similar but some results are contradictory. Cardiac autonomic activity was detected by HRV in all of those studies, whereas our study is the first study, assessing cardiac autonomic activity by using HRT.

As we know from the literature, the results of the most studies assessing cardiac autonomic activity by using HRV are controversial. Ozdemir *et al.* [39] have shown significantly disturbed parasympathetic activity and normal sympathetic activity in same patients with BD. However Aksoyek *et al.* [14] concluded that parasympathetic tonus was decreased and sympathetic tonus was increased significantly. Beside this Kirimli *et al.* [40] did not detect any significant disturbance of cardiac autonomic nervous system in BD patients.

Both Ozdemir *et al.* and Aksoyek *et al.* detected significant disturbances of cardiac autonomic activities in BD. However Kirimli *et al.* did not detect any abnormality of the cardiac autonomic nervous system in BD. Our results were in consistent with the results of Kirimli *et al.*

We also found that normal cardiac autonomic activity (via HRT) is consistent with Kirimli *et al.* But our results were different from the other two studies. The First factor is the methodologic differences which may contribute to this contradiction. We evaluated the cardiac autonomic activity via HRT whereas previous three studies evaluated it via HRV. As it is known that HRV and HRT are complementary indicators of cardiac autonomic activity. Either may be normal while the other one is abnormal [37]. Another possible explanation may be the duration of disease. Our patients had a history of average 7 years of BD. The third factor was constitutional and genetic factors which may also play a role in these different results.

The main limitation of our study was the small sample size. The HRT method used in our study could calculate the TO and TS parameters in only half of the patients. Since the HRT parameters should not be calculated in patients without VPB in their Holter recordings. Therefore, the precision of determining HRT will vary depending on the number of VPBs analyzed. The other limitation of our study is the unknown inflammation levels of the patients.

5. Conclusion

Consequently, HRT parameters determining the cardiac autonomic dysfunction did not seem to be altered in patients with Behcet's disease. Comprehensive studies related to cardiac autonomic function must be performed in this disease. In addition, these findings need to be confirmed with larger studies.

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Abbreviations

BD: Behçet's disease
 HRT: Heart rate turbulence
 ISGC: International Study Group Criteria
 TO: Turbulence onset
 TS: Turbulence slope
 HRV: Heart rate variability
 BRS: Baroreflex sensitivity
 VPB: Ventricular premature beat
 SEM: Standard error of mean

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