# A New Cardiac Autonomic Function Predictor (Heart Rate Turbulence) in Patients with Ankylosing Spondylitis

## *Ankilozan Spondilitte Yeni Bir Kardiyak Otonomik Belirteç: Heart Rate Turbulence*

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**Abstract**

**Objective:** Ankylosing spondylitis (AS) is a chronic systemic disease. The risk of cardiovascular morbidity and mortality is high in patients with AS. Heart rate turbulence (HRT) expresses ventriculophasic sinus arrhythmia and has been considered to reflect cardiac autonomic activity. It has been shown that HRT is an independent and powerful predictor of mortality. The aim of this study was to determine HRT changes in patients with AS in comparison with healthy controls.

**Materials and Methods:** Thirty-seven patients with AS (28 men, 9 women; age: 42±2 years, range: 19-69 years) according to the modified New York criteria and 37 age-and gender-matched healthy control subjects without obvious cardiovascular disease (mean age: 40±2 years, range: 23-68 years) were included in this study. Mean duration of AS was 5±3 years (range: 1-20 years). All participants underwent 24-hour Holter ECG. HRT measurements, turbulence onset (TO) and turbulence slope (TS) were calculated with HRT View Version 0.60-0.1 software program. HRT was calculated in patients and healthy controls with at least one ventricular premature beat (VPB) in their Holter recordings. TO is a measure of the early sinus acceleration and TS is the measure of the rate of sinus deceleration that follows the sinus acceleration after a VPB.

**Results:** There were no significant differences in TO and TS between AS patients and control subjects (TO-AS: -0.0004±0.008, TO-Control: -0.118±0.006; TS-AS: 12.07±1.26, TS-Control: 10.39±1.26, respectively).

**Conclusion:** Although cardiovascular manifestation (including increased morbidity and mortality) of AS has been shown in various studies, HRT parameters, which determine the risk of sudden death, do not seem to be altered in this disease.

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**Key words:** Autonomic nervous system, heart rate turbulence, baroreflex sensitivity, ankylosing spondylitis

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**Özet**

**Amaç:** Kronik sistemik bir hastalık olan ankilozan spondilitte (AS), kardiyovasküler mortalite ve morbidite yüksektir. Ventrikülofazik sinüs aritmisini yansıtan heart rate turbulence (HRT), kardiyak otonomik aktiviteyi göstermektedir. HRT mortaliteyi belirlemede bağımsız ve güçlü bir belirleyicidir. Bu çalışmanın amacı AS'li hastalarda HRT parametrelerinin saptanması ve sağlıklı bireyler ile karşılaştırılmasıdır.

**Yöntem ve Gereçler:** Hasta grubunu, New York kriterlerine gore AS tanısı konan 37 hasta oluşturdu (28 erkek, 9 kadın; ort. yaş: 42±2, yaş aralığı: 19-69). Kontrol grubunu ise cinsiyet ve yaş yönünden hasta grubuna benzer ve bilinen kardiyovasküler hastalığı olmayan, 37 sağlıklı birey oluşturdu (ort. yaş: 40±2 yaş aralığı: 23-68). Hastalar, ortalama 5±3 yıldır AS tanısı ile takip edilmekteydi. Çalışmaya katılan tüm bireylerin 24 saatlik Holter kayıtları alındı. HRT parametreleri turbulence onset (TO), ve turbulence slope (TS), olarak HRT View Version 0.60-0.1 software program ile hesaplandı. HRT, Holter kayıtlarında en az 1 ventriküler erken vurusu olan hastalarda ve sağlıklı bireylerde hesaplandı. TO VPB sonrası erken sinus hızlanmasının, TS ise VPB sonrası sinus hızlanmasını takip eden sinus yavaşlamasının ölçütüdür.

**Bulgular:** Ankilozan spondilitteli hastalar ile sağlıklı bireylerin TO ve TS değerleri benzer olarak bulundu, (TO-AS: -0.0004±0.008, TO-kontrol: -0.118±0.006; TS-AS: 12.07±1.26, TS-kontrol: 10.39±1.26).

**Sonuç:** Birçok çalışmada AS'li hastalarda artmış morbidite ve mortaliteyi içeren kardiyovasküler tutulumlar gösterilmiş olmasına rağmen, ani ölümü belirleyebilen HRT parametreleri AS li hastalarda değişmiyor gibi görünmektedir.

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**Anahtar sözcükler:** Otonomik sinir sistemi, heart rate turbulence, barorefleks sensitivitesi, ankilozan spondilit

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## Introduction

Ankylosing spondylitis (AS) is a chronic and inflammatory disease in which especially spine and sacroiliac joints are included. Cardiac and neurologic manifestations represent some of the extra-skeletal involvements of AS (1, 2). Conduction system abnormalities (3, 4), valvular diseases (5, 6), diastolic dysfunction (7), and pulmonary hypertension (8) are some of the various cardiac manifestations. Although these cardiac involvements may be seen in patients with AS in the absence of clinical manifestations, cardiovascular death in patients with AS is higher than in the general population (9, 10).

Studies investigating the cardiac autonomic function in AS are limited and controversial. Yildirir et al. (11) found no evidence of cardiac autonomic involvement in patients with AS, whereas Toussirot et al. (12) showed that there was a decrease in parasympathetic activity of the heart as evidenced by higher heart rate and lower baroreflex slope in patients with AS. These alterations in autonomic activity of the heart may play a key role in high cardiovascular death in patients with AS. There are some noninvasive predictive parameters for detecting the cardiac autonomic function, such as heart rate variability (HRV), baroreflex sensitivity (BRS) and heart rate turbulence (HRT). All of these tests assess the autonomic and reflex modulations of cardiac function.

It has been shown that deterioration of HRT is correlated with BRS impairment. HRT deterioration reflects cardiac autonomic dysfunction (13). HRT expresses ventriculophasic sinus arrhythmia, i.e., the early acceleration and the late deceleration of sinus rhythm after single VPB (ventricular premature beat), and it is considered to reflect autonomic nervous system function. It has been shown that HRT is an independent and powerful predictor of mortality and sudden cardiac death in various cardiac abnormalities (14, 15).

In this study, our aim was to evaluate cardiac autonomic function, which may be responsible for the higher cardiovascular death in AS, using the HRT method. According to the literature, there has been no previous study about HRT parameters in patients with AS.

## Materials and Methods

### Study Participants

Thirty-seven patients with AS (28 men, 9 women; age: 42±2 years, range: 19-69 years) who fulfilled the 1984 modified New York criteria (16) and 37 age- and gender-matched healthy control subjects without obvious cardiovascular disease (mean age: 40±2 years, range: 23-68 years) were included in this study. Mean disease duration was 5±3 years (range: 1-20 years). The 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) were excluded as well as those who were smokers or using cardioactive drugs (especially beta- blockers and/or antiarrhythmic drugs). All participants' physical examinations and resting 12-lead electrocardiograms (ECGs) 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.

### HRT Analysis

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 HRT, abnormal beats and areas of artifact, which were accepted as VPB by computer, were manually identified and excluded. Measurements of HRT were calculated by the original method, performed by Schmidt et al. (14), as shown in Figure 1. TO, which is a measure of the early sinus acceleration after a VPB, is expressed as a percentage and is calculated with the following formula: $[(RR_1+RR_2) - (RR_{-2}+RR_{-1})]/(RR_{-2}+RR_{-1}) \times 100$, 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 preceding the VPB.

Turbulence slope (TS) is a measure of the rate of sinus deceleration that follows the sinus acceleration after a VPB. It is accepted as the 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 then averaged, whereas TS was calculated based on an averaged local tachogram.

Before the study, all participants were informed of the trial and provided written informed consent.

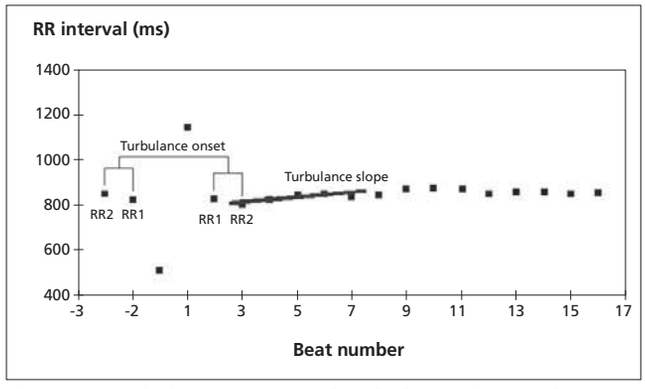


**Figure 1. Turbulence onset and turbulence slope values**

**Statistical Analysis**

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

## Results

All patients completed the study. Demographic properties of the AS and control groups are shown in Table 1. The ECGs were normal in both groups. They were all in sinus rhythms and none of them had pacemaker. HRT parameters, TO and TS did not differ significantly between the two study groups, as seen in Table 2 (TO-AS: -0.0004±0.008, TO-Control: -0.118±0.006; TS-AS: 12.07±1.26, TS-Control: 10.39±1.26, respectively).

**Table 1.** Demographic properties of patient and control groups

| | AS Group (n=37) | Control Group (n=37) | p |
|---|---|---|---|
| Age (years) | 42±2 | 40±2 | NS |
| Male/Female | 28/9 | 28/9 | NS |
| Hear Rate | 74±3 | 76±2 | NS |
| Systolic Blood Pressure | 128±4 | 125±3 | NS |
| Diastolic Blood Pressure | 76±2 | 74±3 | NS |

Values are n or mean±SEM, NS: Not significant, AS: Ankylosing spondylitis

**Table 2.** Turbulence onset/slope of patient and control groups

| | AS Group (n=37) | Control Group (n=37) | p |
|---|---|---|---|
| TO | -0.0004±0.008 | 0.118±0.006 | NS |
| TS | 12.07±1.26 | 10.39±1.14 | NS |

Values are n or mean±SEM, NS: Not significant, TO: Turbulence onset, TS: Turbulence slope, AS: Ankylosing spondylitis

## Discussion

The risk of cardiovascular morbidity and mortality is significantly increased in patients with AS, when compared to the general population (9, 10). This is evidenced by a higher incidence of congestive heart failure, valvular diseases, coronary artery diseases, peripheral vascular diseases, and left ventricular hypertrophy (17-19). However, it has been shown in only one study that patients with AS did not have excess mortality when compared with the general population (20).

It was thought that the possible reasons for increased cardiovascular mortality in AS are accelerated atherosclerosis, left ventricular hypertrophy and diastolic dysfunction associated with congestive heart failure.

There are several factors that are responsible for accelerated atherosclerosis, including endothelial dysfunction (decreased arterial compliance and increased intima-media thickness) (21, 22), elevated levels of prothrombogenic factors (fibrinogen, von Willebrand factor, platelets, and subnormal fibrinolytic blood activity) (20) and systemic chronic inflammation (higher interleukin 6 and C-reactive protein [CRP]) (23, 24). These factors are accepted as non-traditional cardiovascular risk factors playing a synergistic role in the atherosclerotic process in AS.

The investigators of the LIFE study have shown that left ventricular hypertrophy without coronary artery disease was associated with increased likelihood of subsequent cardiovascular events (25). In various studies, it has been shown that diastolic dysfunction and left ventricular hypertrophy were seen in patients with AS. Diastolic dysfunction in patients with AS was determined by echocardiography and histopathologic examination (6, 7, 26).

The other possible reason for cardiovascular mortality can be congestive heart failure. Han et al. (17) showed that there was an increased prevalence ratio of congestive heart failure in AS.

Coronary artery disease, left ventricular hypertrophy and congestive heart failure cause cardiovascular death with associated arrhythmia. BRS and HRT, which are some of the noninvasive prognostic factors showing cardiac autonomic activity, can determine cardiovascular death with associated arrhythmia (27). HRT is interrelated with spontaneous BRS and it may be used in its place as a new diagnostic method (27). It is proven that HRT also predicts mortality and sudden cardiac death in various cardiac abnormalities (14, 28-30).

The heart is richly innervated by afferent and efferent vagal and sympathetic fibers and is thus susceptible to autonomic influences (23). Changes in efferent cardiac autonomic traffic to the heart play a critical role in the genesis and outcome of cardiac arrhythmias and also sudden death. Increased sympathetic and decreased vagal tone can interact with all of the electrophysiological mechanisms underlying arrhythmogenesis. Efferent cardiac autonomic activity is largely under the control of baroreceptor and BRS, which is correlated with cardiac arrhythmias (29, 30).

Heart rate turbulence (HRT) is highly correlated with spontaneous BRS (28). It is proven that HRT also predicts mortality and sudden cardiac death in various cardiac abnormalities like in the postmyocardial infarction period (14), after coronary artery by-pass grafting surgery (31) and in chronic heart failure (32). In addition, HRT predicts alterations in cardiac autonomic function in diabetes mellitus (33) and hyperthyroidism (34). HRV was also changed in these diseases (35-37). Most of the studies determined that HRT, BRS and HRV were wrecked in the same diseases. However, they can not change together in the same disease. For example, Bigger et al. (38) showed an altered HRV after myocardial infarction; BRS and HRT

were found as normal in the same patient population. Bigger et al. also demonstrated that there was a weak correlation between BRS and Holter measures of HRV in myocardial infarction. Furthermore, Ortak et al. (39) showed that indices of HRV increased 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 aspect of the autonomic nervous system activity and they might provide prognostic information of incremental value.

In previous studies, HRV was determined in patients with AS; however, HRT has not been investigated as yet. Toussirot et al. (12) observed a decreased parasympathetic activity in patients with AS by using HRV. They suggested that this autonomic strain may be related to the cardiac involvement in AS patients. On the contrary, Yildirir et al. (11) determined no evidence of autonomic nervous system involvement in patients with AS by HRV analysis.

Toussirot et al. (12) showed the association of AS with cardiac autonomic dysfunction. On the contrary, in our study, the component of the cardiac autonomic function that was determined by HRT did not seem to be altered in patients with AS. It is difficult to explain the different results in the two studies involving cardiac autonomic function in AS. This may be due in part to methodological discrepancies or it could possibly reveal heterogeneity in the cardiac autonomic nervous system in patients with AS. Constitutional and genetic factors may also play a role in these different results.

Heart rate turbulence (HRT) could be influenced by the underlying heart rate. Recently, Bauer et al. (40) investigated the relationship between HRT and the underlying heart rate.

The main limitation of our study seems to be the small sample size. The HRT method that we used in the study could calculate TO and TS parameters in approximately half of the patients. 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 absence of inflammation levels of the patients.

## Conclusion

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

**Conflict of Interest**
No conflict of interest declared by the authors.

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