Cardiac autonomic function in patients with rheumatoid arthritis: heart rate turbulence analysis

Romatoid artritli hastalarda kardiyak otonomik fonksiyonlar: Kalp hızı türbülansı analizi

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ABSTRACT

Objective: Rheumatoid arthritis (RA) is a chronic systemic disease. The risk of cardiovascular morbidity and mortality is high in patients with RA. 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 is to determine if HRT changes in patients with RA in comparison with the healthy controls.

Methods: The study was performed as a cross-sectional study. Twenty-six patients with RA (mean age 56±10 years, 18 women) and 26 healthy controls (mean age 55±9 years, 18 women) were enrolled in this study. All participants underwent 24 hours Holter electrocardiogram monitoring. HRT measurements, turbulence onset (TO) and turbulence slope (TS), were calculated in patients and healthy controls that have at least one ventricular premature complex (VPC) 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 VPC. Mann-Whitney U test was used for comparison of continuous variables and the Chi-square test for comparison of categorical variables.

Results: There were no statistically significant differences in TO and TS between the RA and control groups (TO: -2.2±3.1% vs -2.8±2.5%, p=0.25; TS: 11.5±9.7 ms/RR vs 15.5±10.9 ms/RR, p=0.10).

Conclusion: HRT parameters, which determine the autonomic dysfunction, did not seem to be altered in patients with RA.

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Key words: Autonomic nervous system, heart rate turbulence, ventricular premature complex, rheumatoid arthritis, Holter electrocardiogram

ÖZET


Yöntemler: Çalışma, enine-kesitli bir çalışma olarak planlandı. Çalışma, RA hastalarından (ortalama yaş 56±10 yıl, 18 kadın) ve sağlıklı kontrol grubundan (ortalama yaş 55±9 yıl, 18 kadın) toplam 52 kişiden oluşmaktadır. Tüm katılımcılara 24 saat Holter elektrokardiyogramu uygulandı. HRT parametreleri olan türbülans başlangıcı (TO) ve türbülans eğimi (TS), Holter kayıtlarında en az bir adet ventriküler erken vuruş (VEV) olanlardan hesaplandı. TO, VEV sonrası oluşan erken sinüs hıysaştırıcıya, TS ise, bu hırsızın sonrakında gelişen sinüs yavaşlamasına bir ölçüsüdür. Çalışmanın amacı, RA‘lı hastalardaki olası KHT değişikliklerini sağlıklı gönüllüler ile karşılaştırmaktır.

Bulgular: HKT, ventrikülofasik sinüs arıtımının bir sonucu olup, kardiyak otonomik aktivitenin bir göstergesi olarak kabul edilmektedir. Kalp hızı türbülansının (KHT), mortalitenin güçlü ve bağımsız bir belirteci olduğu gösterilmiştir. Çalışmanın amacı, RA‘lı hastalarda olası KHT değişikliklerini sağlıklı gönüllüler ile karşılaştırmaktır.

Sonuç: Otonomik disfonksiyonun bir göstergesi olan KHT parametreleri RA hastalarında değişmemektedir.

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Anahtar kelimeler: Otonomik sinir sistemleri, kalp hızı türbülansı, ventriküller erken vuruş, romatoid artrit, Holter elektrokardiyogram
Introduction

Rheumatoid arthritis (RA) is a chronic multisystemic disease. RA has various cardiac manifestations including pericarditis (1), conduction system abnormalities (2), coronary arteritis (3), valvular disease (4), aortitis (5), myocarditis (6) and pulmonary hypertension (7). Although cardiac involvement in RA is not always symptomatic, it has been shown that there was a significantly increased mortality ratio due to cardiovascular events (8-10).

Heart rate variability (HRV), baroreflex sensitivity (BRS) and heart rate turbulence (HRT) are noninvasive predictive parameters of sudden death. All of these tests assess the autonomic and reflex modulations of cardiac function. Studies investigating cardiac autonomic function in RA are limited. It has been shown that there was an increase in sympathetic control of the heart rate that could play a key role in development of ventricular tachyarrhythmia, which can cause sudden death in patients with RA (11).

HRT impairment reflects cardiac autonomic dysfunction, in particular, impaired BRS and reduced parasympathetic activity (12). HRT expresses ventriculophasic sinus arrhythmia, i.e. the early acceleration and the late deceleration of sinus rhythm after single ventricular premature complex (VPC), 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 (13). However, few is known on HRT behavior in patients with RA.

In this study, our aim was to evaluate cardiac autonomic function in RA using HRT analysis and compare it with healthy subjects.

Methods

Study participants

The study was performed as a cross-sectional study. Forty-two patients with RA who were already being followed by the Department of Physical Medicine and Rehabilitation and 48 age and sex matched healthy controls were enrolled in this study. The diagnosis of RA was based on 1987 revised criteria of the American Rheumatism Association (14). The patients having 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 are smokers and using cardio-active drugs (especially beta blockers and/or antiarrhythmic drugs). All participants’ physical examinations, resting 12-lead electrocardiograms and exercise tests were normal. Routine biochemical and hematological values including fasting blood glucose, blood urea nitrogen, serum electrolytes, thyroid hormones and hemoglobin levels were within normal ranges. All participants underwent 24 hours Holter electrocardiogram monitoring. HRT could not be calculated in 16 patients with RA and 22 controls that did not have any VPC in their Holter recordings. Therefore, 16 patients with RA and 22 control subjects were excluded from the study. HRT were calculated in 26 patients with RA (mean age 56±10 years, 18 women) and 26 control subjects (mean age 55±9 years, 18 women) who had at least one VPC in their Holter recordings. Before study, all participants were informed of the trial and gave written informed consent, which was approved by the local Ethics committee of our institution.

HRT analysis

All participants underwent 24 hours Holter ECG monitoring. Holter recordings were analyzed with Pathfinder Software Version V8.255 (Reynolds Medical, Hertford, England). Turbulence onset (TO), and turbulence slope (TS) values of HRT were calculated using View Version 0.60-0.1 Software Program (Munich, Germany). While determining HRT, abnormal beats and areas of artifact, which were accepted as VPC by computer were manually identified and excluded. Measurements of HRT were calculated by the original method, performed by Schmidt et al. (13).

TO, which is a measure of the early sinus acceleration after a VPC, is expressed as a percentage and is calculated with the following formula:

\[
\text{TO} = \left(\frac{\text{RR}_1 + \text{RR}_2}{\text{RR}_2 + \text{RR}_1}\right) \times 100,
\]

where RR1 and RR2 are the first and second sinus RR intervals after the VPC, and RR3 and RR4 are the first and the second sinus RR intervals preceding the VPC.

TS is a measure of the rate of sinus deceleration that follows the sinus acceleration after a VPC. It is accepted as the maximal positive slope among all slopes of a series of regression lines obtained from all sequences of 5 consecutive RR intervals (within the first 20 sinus rhythm intervals after a VPC) and expressed as ms/RR.

TO was calculated for all VPC’s separately and then averaged, whereas TS was calculated based on an averaged local tachogram.

Statistical analysis

Statistical analyses were performed with SPSS for Windows version 10.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as percentage (%) or the mean±SD. Comparisons between independent groups were performed using Mann-Whitney U non-parametric test for continuous variables and the Chi-square test for categorical variables. A P value <0.05 was considered as statistically significant.

Results

All patients completed the study. There were no differences in age and gender between two groups (RA group; mean age: 56±10 years, gender: 8 male/18 female, and Control group; mean
age: 55±9 years, gender: 8 male/18 female). The electrocardiograms and exercise tests were normal for two groups. They were all in sinus rhythm and none of them had pacemaker.

HRT parameters, TO and TS did not differ significantly (p>0.05) between two study groups (Table 1 and Fig. 1).

**Discussion**

The results of the present study demonstrate that there were no differences in TO and TS values between patients with RA and controls.

### Table 1. Comparison of heart rate turbulence parameters between patient and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>RA (n=26)</th>
<th>Control (n=26)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO, %</td>
<td>-2.2±3.1</td>
<td>-2.8±2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>TS, ms/RR</td>
<td>11.5±9.7</td>
<td>15.5±10.9</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Values are represented as mean±SD
*Mann-Whitney U test
RA - rheumatoid arthritis, TO - turbulence onset, TS - turbulence slope

Two phases of HRT, the early sinus rate acceleration and late deceleration, are quantified by 2 parameters termed TO and TS. The initial heart rate acceleration (TO) is triggered by transient vagal inhibition in response to the missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction. Both branches of the autonomic nervous system contribute to the late HRT phase (TS). A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment. The HRT pattern is blunted in patients with reduced baroreflex (15).

The risk of cardiovascular morbidity and mortality is significantly increased in patients with RA, when compared to the general population. This is evidenced by a higher incidence of congestive heart failure, coronary artery disease and myocardial infarction (frequently silent), as well as sudden cardiac death (10, 16). In contrast, only one study has shown that patients with RA did not have excess mortality due to acute myocardial infarction compared with general population (17).

It was thought that the possible reason for increased cardiovascular mortality in RA is accelerated atherosclerosis. Non-invasive methods showed that RA patients have endothelial dysfunction, decreased arterial compliance, and increased intima-media thickness, which are associated with atherosclerosis. Traditional cardiovascular risk factors do not seem to be solely responsible for accelerated atherosclerosis. Systemic chronic inflammations, immune suppressive therapy (especially corticosteroids) are non-traditional cardiovascular risk factors playing a synergistic role in atherosclerotic process in RA (18).

The heart is richly innervated by afferent and efferent vagal and sympathetic fibers and is thus susceptible to autonomic influences (19). 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. The efferent cardiac autonomic activity is largely under the control of baroreceptor and baroreflex sensitivity, which are correlated with cardiac arrhythmias (20). HRT is highly correlated with spontaneous baroreflex sensitivity and it may be used instead of baroreflex sensitivity as a new diagnostic method (21). It is proven that HRT also predicts mortality and sudden cardiac death in various cardiac abnormalities like postmyocardial infarction period (13), after coronary artery bypass grafting surgery (22) and in chronic heart failure (23). In addition, HRT predicts alterations of cardiac autonomic function in diabetes mellitus (24) and hyperthyroidism (25). HRV is also impaired in these diseases (26-28). Most of the studies determined that HRT, baroreflex sensitivity and HRV were wrecked in the same diseases. However, they can not always change in the same disease. For example, Bigger et al. (29) have shown that altered HRV has been determined after myocardial infarction; baroreflex sensitivity and HRT were found as normal in the same group. Bigger et al. (29) have shown that there was a weak correlation between baroreflex sensitivity and Holter measures of HRV in
myocardial infarction. Also Ortak et al. (30) showed that in the same patient group after myocardial infarction, indices of HRV increased but parameters of HRT did not change. As a result, HRT and HRV indices may indicate different aspects of the autonomic nervous system activity and they might provide prognostic information of incremental value (29).

In previous studies, HRV in patients with RA was determined; however, HRT has not been investigated yet. Evrengül et al. (11) observed an increase in sympathetic control of the heart rate in patients with RA by using HRV. They suggested that the increased sympathetic activity could play a key role in the development of ventricular tachyarrhythmia and it may be related to the higher incidence of sudden death (11). Contrary in our study, the component of the cardiac autonomic function, which was determined by HRT did not seem to be altered in patients with RA. It is difficult to explain different results of both studies, involving cardiac autonomic function in RA. This may be partly due to methodological discrepancies or possibly reveal heterogeneity in cardiac autonomic nervous system in patients with RA. The constitutional and genetic factors also may play role in these different results. The physiological mechanisms underlying the various measures of HRV and HRT are different. HRV describes variations in both instantaneous heart rate and RR intervals, and can reflect the coupling between the autonomic nervous system and the sinoatrial node. HRT reflects the physiologic biphasic response of the sinus node to VPC’s, most likely because of a baroreflex arc. There is a modest correlation between HRT parameters and HRV measures.

HRT could be influenced by the underlying heart rate. Recently, Bauer et al. (31) investigated the relationship between HRT and underlying heart rate. They utilized data from EMIAT study (31). They have developed a numerical parameter termed turbulence dynamics, which quantifies the relationship between TO and underlying heart rate. This new turbulence parameter was an independent predictor of mortality after acute myocardial infarction. Turbulence dynamics is the newest parameter for cardiac autonomic function.

Study limitations

The main limitation of our study seems to be the small sample size. The HRT method that we used in the study, could calculate turbulence onset and turbulence slope parameters, approximately in half of patients. HRT parameters should not be calculated in patients who did not have VPC in their Holter recordings. Therefore, the precision of determining HRT will vary depending on the number of ventricular premature beats analyzed.

Conclusion

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

Conflict of interest: None declared.

References