

Cardiovascular autonomic neuropathy in rheumatoid arthritis assessed by cardiovascular autonomic function tests: A cross-sectional survey

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ABSTRACT

Objective: In this study, we aimed to evaluate cardiovascular autonomic neuropathy (CAN) in RA patients by cardiovascular autonomic function tests. Because CAN was reported of patients with autoimmune rheumatic diseases those may in sudden death or myocardial infarction.

Methods: A total of 44 patients with RA and 44 age- and sex-matched healthy volunteers participated in this cross-sectional study. Assessment of CAN was performed using cardiovascular reflex tests. These five tests were: 1) beat-to-beat heart rate variation during deep breathing; 2) heart rate response to standing up; 3) heart rate response to the Valsalva maneuver; 4) blood pressure response to standing up; and 5) blood pressure response to sustained handgrip.

Results: The mean age was 43.15 (SD, 12.18) years (range, 23-68 years) in the RA group, and 38 were women. In beat-to-beat heart rate variation during deep breathing, expiration-to-inspiration ratio was abnormal in 3 cases with RA (6.8%) but in 1 (2.3%) control subject ($p=0.3$), and maximum minus minimum heart rate was abnormal in 8 patients (18.2%) and in 3 (6.8%) control subjects ($p=0.1$). 2) In heart rate response to standing up, all patients and controls had normal results. Valsalva ratio was abnormal in 7 RA patients (15.9%) and in 7 control subjects (15.9%). Blood pressure response to standing up was normal in RA patients but abnormal in 1 (2.3%) control subject ($p=0.4$). Blood pressure response to sustained handgrip was abnormal in 5 RA patients (11.4%) and 2 (4.6%) control subjects ($p=0.2$).

Conclusion: Our study failed to show any statistically significant difference between cardiovascular autonomic function tests in RA patients with control subjects by our test done. (*Anatol J Cardiol* 2015; 15: 722-6)

Keywords: rheumatoid arthritis, cardiovascular autonomic neuropathy, cardiovascular autonomic function tests

Introduction

In many chronic diseases, including primary neurological diseases, renal failure, and diabetes mellitus, dysfunction of autonomic nervous system can occur (1).

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disorder of unknown etiology that primarily involves joints. Involvement of the musculo-skeletal system other than joints (eg, muscles and bones), as well as organs not considered part of the musculoskeletal system (eg, bone marrow, lung, heart, kidney, blood vessels, eye, salivary glands, the central and peripheral nervous systems, and skin), occurs in about 40% of patients with RA over a lifetime of disease (2).

Although the involvement of the central and peripheral nervous system is well known in rheumatoid arthritis (RA), knowledge on the involvement of the autonomic nervous system is scarce (3).

Studies about autonomic nervous system (ANS) involvement in RA are limited, with conflicting results. The autonomic nervous system comprises parasympathetic and sympathetic nerves with complementary function (4).

The parasympathetic nervous system reduces heart rate and blood pressure and results in conservation and restoration of energy and the facilitation of digestion and absorption of nutrients. The sympathetic nervous system, on the other hand, enables the body to get prepared for conditions, such as fear or fighting through increasing heart rate, blood pressure, and cardiac output.

Cardiovascular autonomic neuropathy (CAN) is secondary to damaged ANS fibers that innervate the blood vessels and the heart and is associated with abnormalities of vascular dynamics and heart rate control (5).

In different studies, CAN was reported in 24% to 100% of patients with autoimmune rheumatic diseases. In these patients,

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CAN may result in significant complications, such as sudden death and myocardial infarction (1).

Cardiovascular autonomic function tests that are commonly used to detect CAN include a number of simple objective tests of cardiovascular autonomic function and reflexes that we can use for the diagnosis of cardiovascular autonomic neuropathy (6).

To the best of our knowledge, CAN in RA is not clearly understood. In this study, we aimed to evaluate CAN in patients with RA through cardiovascular autonomic function tests. We used age- and sex-matched healthy controls, as ANS function deteriorates with age.

Methods

Patients

In this cross-sectional study, 44 patients with RA who fulfilled the American College of Rheumatology criteria for the diagnosis of RA that received their usual care in the rheumatology clinic of Shariati hospital (Tehran University of Medical Sciences), Tehran, Iran, were recruited from December 2011 through September 2012.

Patients were excluded if they had any of the following conditions: anemia; any disease interfering with the autonomic nervous system, including diabetes mellitus, renal and liver diseases, Parkinson's disease, porphyria, and amyloidosis; cardiovascular diseases, including hypertension, ischemic heart disease, congestive heart failure, valvular heart disease, cardiomyopathy, and cardiac arrhythmia; neurological diseases, including polyneuropathy, multiple sclerosis, and Guillain-Barre syndrome; pregnancy; and thyroid disorders. Individuals taking drugs that interfered with the ANS, including vasodilators, anti-arrhythmics, sedatives, diuretics, aspirin, adrenergic blockers, antidepressants, antiepileptic and hypnotic drugs, and antihistamines, were also excluded (7).

Tobacco, caffeine, and medications were not allowed before the tests.

All subjects (case and control group) were assessed under stable vital signs. The project was approved by the ethics committee of Tehran University of Medical Sciences and was performed in accordance with the Declaration of Helsinki. All subjects were fully informed about the purpose of the study and gave their informed consent to participate.

In this study, 44 age- and sex-matched healthy volunteers acted as controls. Clinical and demographic information was obtained through a structured interview. CAN was assessed by a battery of noninvasive tests, applying cardiovascular reflex tests according to Ewing et al. (6).

All tests were performed under standardized conditions in the morning by a trained person. All controls and patients were evaluated to have normal sinus rhythm without any conduction defect in a standard electrocardiogram. All electrocardiogram (ECG) tracings were done by (CAREWELL electrocardiograph, ECG-1101, 50 fdHz/60Hz).

The five tests used in our study were: 1) beat-to-beat heart rate variation during deep breathing; 2) heart rate response to

standing up; 3) heart rate response to the Valsalva maneuver; 4) blood pressure response to standing up; and 5) blood pressure response to sustained handgrip. The test of predominantly parasympathetic integrity is heart rate variability to deep breathing. Tests of predominantly sympathetic integrity are the Valsalva ratio, postural systolic blood pressure falls, and blood pressure response to sustained handgrip. Although both sympathetic and parasympathetic innervation plays some part in all five tests (8, 9). The results of all tests were added, and total scores of the overall test were computed. Zero was considered totally normal. The overall test was defined as abnormal if at least one test was abnormal.

In the first test (beat-to-beat heart rate variation during deep breathing), the participants lay quietly and breathed deeply at a rate of 6 breaths per minute (a rate that produces maximum variation in heart rate) while heart rate was recorded by ECG tracing.

We used visual cues to guide inspiration and expiration for standardizing the breathing rate. A cardiologist assessed ECG tracings to calculate expiration-to-inspiration ratio (the ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration).

The time intervals between R waves of the QRS complexes were measured in milliseconds. The lowest normal value for participants aged between 20-24 years was 1.17, 1.15 for 25-29 years, 1.13 for 30-34 years, 1.12 for 35-39 years, 1.10 for 40-44 years, 1.08 for 45-49 years, 1.07 for 50-54 years, 1.06 for 55-59 years, 1.04 for 60-64 years, 1.03 for 65-69 years, and 1.02 for 70-75 years (5).

Also, based on different measurement of R-R variation, we calculated differences between the maximum and minimum heart rates. In normal subjects, the maximum-minimum heart rate was ≥ 15 beats/min.

In the second test (heart rate response to standing up), evaluation of the cardiovascular response to a change from horizontal to vertical position was evaluated. The patients were connected to an electrocardiogram monitor while lying down and then standing to a full upright position.

ECG tracings were assessed by the same cardiologist to determine the 30:15 ratio [the ratio of the longest R-R interval (about beat 30) to the shortest R-R interval (about beat 15)]. Ziegler et al. (10) redefined the 30:15 ratio to beats 20-40 as the longest R-R interval divided by beats 5-25 as the shortest R-R interval, because max/min R-R intervals may not always occur exactly at the 15th or 30th beat after standing. Therefore, in the reevaluation of ECG tracings, this point was considered. The normal ratio is ≥ 1.04 .

The third test: Heart rate responses to the Valsalva maneuver (Valsalva ratio)

The Valsalva maneuver, with its complex effect on cardiovascular function, is the basis of its usefulness as a measure of autonomic function. During the sitting position, the participants were connected to an ECG monitor and forcibly exhaled for 15 s into a mouthpiece at a constant pressure of 40 mm Hg.

The heart rate normally increases during the maneuver, followed by rebound bradycardia after release.

The Valsalva ratio was calculated by the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during or shortly after the maneuver from the ECG tracings. The normal Valsalva ratio is ≥ 1.2 .

The fourth test: Blood pressure response to active change of posture

Participants were resting in the supine position for 10 min and then asked to stand up for 3 min. The systolic blood pressure was measured just before standing and 3 min after active standing.

A response was considered abnormal if systolic blood pressure decreased more than 30 mm Hg within 3 min after standing. Blood pressure was measured automatically by a (Apple KD-591) blood pressure monitor.

The last test was diastolic blood pressure response to sustained handgrip.

In this test, sustained muscle contraction was performed using a handgrip dynamometer. The sustained handgrip was performed using a hydraulic hand dynamometer (SAEHAN, SH5001).

The dynamometer is squeezed to isometric maximum and then held at 30% of maximum for 5 min. The absolute difference between the highest diastolic blood pressure during handgrip and the basal diastolic blood pressure just before the handgrip is recorded. The abnormal response is a rise of diastolic blood pressure < 10 mm Hg.

Statistical analysis

Continuous data are expressed as mean (SD), and categorical data are presented as number (%). Duration of the disease was expressed as median (interquartile range (IQR) and tested for normality by Kolmogorov-Smirnov test, and due to lack of normality, the association between this variable with test results was assessed by Mann-Whitney U test. The association between categorical variables was assessed by chi-square tests. For all tests, $p < 0.05$ was considered significant. Statistical analysis was performed by SPSS, version 16 software.

Results

A total of 44 RA patients and 44 controls consented to participate in the study. In the RA group, the mean age was 43.15 (SD: 12.18) years, and 38 (86.4%) patients were female. In the control group, the mean age of subjects was 39.5 (SD: 10.98) years, and 39 subjects were female. The mean age did not differ significantly between the control subjects and the patients ($p = 0.14$). All patients and control subjects had none of the exclusion criteria that were a factor for CAN.

The mean resting heart rate was 78 (SD: 11) bpm in RA patients and 74 (SD: 10) bpm in controls, which was not statistically significant different ($p = 0.3$). The median duration of RA was 8.85 years (IQR: 3.5-12).

Assessment of CAN tests in 44 patients with RA Beat-to-beat heart rate variation during deep breathing

A: Expiration-to-inspiration ratio

In patients with RA, the E/I ratio had an abnormal result in 3 cases (6.8%).

The mean E/I ratio was 1.35 (SD, 0.21), the max E/I ratio was 2.25, and the min E/I ratio was 0.8.

B: Maximum minus minimum heart rate [beats/min (bpm)]

This test was abnormal in 8 patients (18.2%). The mean maximum minus minimum heart rate was 22.5 (SD, 12.48), with a max and min of 69 and -13 bpm, respectively.

Heart rate response to standing up

All patients with RA had a normal heart rate response to standing up. The mean heart rate response to standing up was 1.28 (SD, 0.21), with a max of 2.13 and min of 1.06.

Heart rate response to the Valsalva maneuver (Valsalva ratio)

Valsalva ratio was abnormal in 7 (15.9%) patients. The mean Valsalva ratio was 1.5 (SD, 0.3) with a max of 2.7 and a min of 1.06.

Blood pressure response to standing up

This test was normal in all RA patients. The mean blood pressure response to standing up was 2.13 (SD, 5.18), with a max of 19.5 and a min of -8.

Blood pressure response to sustained handgrip

Five patients (11.4%) had an abnormal blood pressure response to sustained handgrip. The mean blood pressure response to sustained handgrip was 19.75 (SD, 4.21), with a max of 28 and a min of 6.

Comparison of CAN tests in the RA patients and control subjects

The CAN test results were compared in the two groups and are summarized in Table 1.

Expiration-to-inspiration ratio was abnormal in 3 patients with RA (6.8%) but only in 1 of the control subjects (2.3%). The difference in the E/I ratio was not statistically significant ($p = 0.3$).

Maximum minus minimum heart rates were abnormal in 8 RA patients (18.2%) and 3 controls (6.8%). There was a difference between the two groups, but it was not statistically significant ($p = 0.1$).

All patients and control subjects had a normal heart rate response to standing up. Heart rate response to the Valsalva maneuver (Valsalva ratio) was abnormal in 7 RA patients (15.9%) and in 7 control subjects (15.9%). There was no difference between the two groups. Blood pressure responses to standing up were normal in RA patients but abnormal in 1 control subject (2.3%) ($p = 0.4$).

Blood pressure responses to sustained handgrip were abnormal in 5 RA patients (11.4%) and in 2 control subjects (4.6%). The difference between the two groups was not statistically significant ($p = 0.2$). Also, 10 controls (22.7%) and 17 patients (38.6%) had at least 1 abnormal test. The difference, however, was not statistically significant (p value > 0.05). Further, 8 of 10

Table 1. Comparison of CAN tests in the RA patients and control subjects

Cardiovascular autonomic neuropathy tests	RA patients (n=44)	Control subjects (n=44)	P
Expiration-to-inspiration ratio no. (%)			
Normal	41 (93.2%)	43 (97.7%)	0.3
Abnormal	3 (6.8%)	1 (2.3%)	
Heart rate response to standing up			
Normal	44 (100%)	44 (100%)	-
Abnormal		0 (0%)	0 (0%)
Maximum minus minimum heart rate			
Normal	36 (81.8%)	41 (93.2%)	0.1
Abnormal	8 (18.2%)	3 (6.8%)	
Valsalva ratio			
Normal	37 (84.1%)	37 (84.1%)	-
Abnormal	7 (15.9%)	7 (15.9%)	-
Blood pressure responses to standing up			
Normal	44 (100%)	43 (97.7%)	0.4
Abnormal	0 (0%)	1 (2.3%)	
Blood pressure response to sustained handgrip 0.78			
Normal	39 (88.6%)	42 (95.4%)	0.2
Abnormal	5 (11.4%)	2 (4.6%)	

Table 2. Association between disease duration and results of tests

Tests	Disease duration (year)		P
	Median	IQR	
Expiration-to-inspiration ratio			
Normal	8.5	7	0.04
Abnormal	2	5	
Maximum minus minimum heart rate			
Normal	9.5	7.5	0.004
Abnormal	2	5	
Valsalva ratio			
Normal	8	9	0.73
Abnormal	8	10.25	
Blood pressure response to sustained handgrip			
Normal	8	9	0.78
Abnormal	7	12	

cases in the control group had 1 abnormal test, and 2 of them had 3 abnormal tests; 11 of the RA patients had 1 and 6 of them had 2 abnormal CAN tests.

The correlation between RA duration and the test results are shown in Table 2.

There was no association between abnormal CAN test results (Valsalva ratio and blood pressure response to sustained handgrip) and disease duration. Beat-to-beat heart rate varia-

tion during deep breathing test (expiration-to-inspiration ratio and maximum minus minimum heart rate), on the other hand, was significantly influenced by the duration of the disease.

The median (IQR) duration of RA in subjects with and without CAN was 6 (2-10) and 10 (4-13.5) years, which was not statistically significant ($p=0.06$).

Discussion

Cardiovascular autonomic neuropathy with significant complications, such as myocardial infarction and significant arrhythmia, can lead to increased cardiovascular morbidity and mortality (5). Therefore, it is important to evaluate CAN in chronic diseases, such as RA. In the present study, we assessed CAN in RA patients compared to control subjects. CAN was made based on several noninvasive cardiovascular tests according to Ewing (6). These tests included beat-to-beat heart rate variation during deep breathing, heart rate response to standing up, Valsalva ratio, blood pressure response to standing up, and blood pressure response to sustained handgrip. The test of predominantly parasympathetic integrity is heart rate variability to deep breathing. The tests of predominantly sympathetic integrity are Valsalva ratio, postural systolic blood pressure fall, and blood pressure response to sustained handgrip. Although both sympathetic and parasympathetic innervation plays some part in all five tests (8, 9).

The major finding of our study was that in the comparison of each of the cardiovascular autonomic function tests in the RA patients with control subjects, there was no statistically significant difference between the two groups. Also, when we compared overall test results in RA patients with control subjects, there was no statistically significant difference between the two groups.

Our study demonstrated that except for blood pressure response to standing up, which was normal in all RA patients, other tests had abnormal results in RA patients. On the contrary to our results, previous studies have shown significant differences in the results of cardiovascular reflex tests between RA patients and healthy individuals (10-13). Louthernoo et al. (7) demonstrated that in patients with RA, compared with controls, the heart rate variation in response to deep breathing was significantly decreased ($p=0.001$). Stojanovich et al. (14) reported that abnormal cardiovascular reflex tests were significantly higher among RA patients than controls ($p<0.05$). In another study by Aydemir et al. (3), a higher prevalence of cardiac autonomic neuropathy was reported in patients compared with controls ($p<0.001$).

Our study also demonstrated that there is no relation between abnormal CAN test results (Valsalva ratio and blood pressure response to sustained handgrip) in RA patients with disease duration, but there is a relation between RA duration and results of beat-to-beat heart rate variation during the deep breathing test (expiration-to-inspiration ratio and maximum minus minimum heart rate). Other studies by Stojanovich et al. (14) and

Aydemir et al. (3) showed that there is no correlation of disease duration with cardiac autonomic neuropathy.

Since not work has been done in this area, we may not be able to completely explain the different results of the studies. Also, the different results may be due to the limitations of the study.

Study limitations

To some degree, our study is limited by several factors. In our study, we were able to recruit patients only from a single academic institution (as the most important ambulatory care clinic); therefore, our samples had regular follow-up and good compliance for treatment and maybe did not have enough progressed disease to appropriately detect differences between patients and control subjects. Another limitation is that the control group and RA group were quite small, and the sample size may not be enough to detect significant differences between patients and control groups (which may have reduced the power of the study).

Another limitation of this study was its cross-sectional nature, which does not demonstrate causal association. The severity of disease, seropositivity, and the treatment feature can contribute to extra-articular complications but were not assessed in this study.

The last limitation is that the more subtle abnormalities in cardiovascular autonomic regulation may be difficult to detect by our those reflex test methods.

Therefore, large prospective cohort studies with more sensitive tests are needed to point out the differences between the cardiovascular autonomic function of RA patients and general population.

Conclusion

Our study failed to show any statistically significant difference between cardiovascular autonomic function tests in RA patients with control subjects.

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