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QTC INTERVAL AND DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS.

INTERVALO QTC E ATIVIDADE DE DOENÇA NA ARTRITE REUMATÓIDE

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Introdução: A Artrite Reumatoide (AR) é uma doença inflamatória crônica autoimune que compromete principalmente as articulações, mas também pode provocar manifestações sistêmicas graves, reduzindo a qualidade e a expectativa de vida. Dentre as manifestações sistêmicas dessa doença destacam-se complicações cardiovasculares, como arritmias e prolongamento do intervalo QT, atribuídas à ação de citocinas inflamatórias sobre o sistema nervoso autônomo e os cardiomiócitos. Essas alterações aumentam o risco de morte súbita em pacientes com AR, ressaltando a importância de estudos que investiguem a relação entre a atividade inflamatória da doença e alterações eletrocardiográficas como o prolongamento do intervalo QT. **Objetivos:** Avaliar a prevalência de prolongamento do intervalo QT corrigido pela frequência cardíaca (QTc) e sua possível associação com a atividade inflamatória em pacientes com AR. **Métodos**: Estudo observacional transversal com 97 adultos portadores de AR atendidos em ambulatório de Reumatologia de um hospital universitário em Curitiba (PR). Foram coletados dados demográficos, clínicos, terapêuticos e índices de atividade da doença (DAS-28 VHS/PCR, CDAI, SDAI). O QTc foi calculado a partir de eletrocardiogramas de 12 derivações utilizando a fórmula de Bazett. **Resultados:** A amostra foi composta predominantemente por mulheres de meia-idade (mediana 63 anos), com tempo de doença de 11 anos. A mediana do QTc foi 410 ms (IIQ = 387,5–437,0), e 11/97 pacientes (11,3%) apresentaram QTc prolongado. Não se observaram correlações significativas entre QTc ou frequência cardíaca e VHS, PCR, DAS-28, CDAI ou SDAI ($p > 0,05$ para todas as comparações). **Conclusão:** Embora o prolongamento do QTc seja relativamente frequente em pacientes com AR, neste estudo não houve evidência de associação com a atividade inflamatória medida pelos principais índices clínico-laboratoriais.

Palavras chave: Artrite Reumatoide, Eletrocardiograma, Arritmias Cardíacas.

ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disease that primarily affects the joints but can also cause severe systemic manifestations, reducing both quality of life and life expectancy. Among the systemic manifestations of this disease, cardiovascular complications—such as arrhythmias and prolonged QT interval—stand out, attributed to the action of inflammatory cytokines on the autonomic nervous system and cardiomyocytes. These alterations increase the risk of sudden death in RA patients, highlighting the importance of studies investigating the relationship between disease inflammatory activity and electrocardiographic changes such as QT interval prolongation. **Objectives:** To assess the prevalence of heart rate-corrected QT interval (QTc) prolongation and its possible association with inflammatory

activity in patients with Rheumatoid Arthritis (RA). **Methods:** Cross-sectional observational study with 97 adult RA patients followed at the Rheumatology outpatient clinic of a university hospital in Curitiba (PR), Brazil. Demographic, clinical, therapeutic data, and disease activity scores (DAS-28 ESR/CRP, CDAI, SDAI) were collected. QTc was calculated from 12-lead electrocardiograms using Bazett's formula. **Results:** The sample consisted predominantly of middle-aged women (median age 63 years) with a disease duration of 11 years. The median QTc was 410 ms (IQR = 387.5–437.0), and 11 out of 97 patients (11.3%) presented prolonged QTc. No significant correlations were found between QTc or heart rate and ESR, CRP, DAS-28, CDAI, or SDAI ($p > 0.05$ for all comparisons). **Conclusion:** Although QTc prolongation is relatively frequent in patients with RA, this study found no evidence of an association with inflammatory activity as measured by major clinical-laboratory indices.

Keywords: Rheumatoid Arthritis, Electrocardiogram, Cardiac Arrhythmias.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease in which the immune system causes an inflammatory process that damage and destroy the patient's joints and connective tissues through the erosion of bones and cartilage. Although the disease primarily affects the joints causing joint deformity, systemic manifestations are very common, significantly reducing quality and life expectancy due to the possibility of affecting various organs. RA affects about 1% of the global population, being two to three times more prevalent in women, with the first symptoms typically appearing between the ages of 35 and 50.[1]

The etiology of RA is unknown; however, it is believed to have a multifactorial origin, with genetic predisposition combined with external factors being the main causes of the disease.

In addition, immune responses to infections may act as triggers for the activation of RA in previously healthy patients who had a predisposition to the disease. Other predisposing factors for the development of RA include smoking, alcohol use, obesity, and hormonal imbalances.[1,2] With a gradual onset, RA typically presents as a polyarticular disease, with early symptoms such as joint stiffness and pain, accompanied by swelling. Patients with poorly controlled disease usually experience progressive joint damage, which may result in significant joint deformities and functional impairment.[3,4]

The diagnosis involves several steps. The evaluation begins with clinical findings, as the disease presents with a characteristic symptom pattern. This is followed by various serological tests to identify antibodies associated with RA, as well as radiological exams to detect possible joint erosions. In some cases, a sample of synovial fluid is also collected for tests that help determine compatibility with RA.[5,6]

As a systemic disease, RA can affect various organs, and significant cardiac changes may occur in these patients. The development of cardiac rhythm disorders, heart failure, pericarditis, and coronary artery disease is more prevalent in RA patients than in the general population, contributing to higher mortality rates in these individuals.[7,8]

Among the cardiac arrhythmias found in RA is the QT interval prolongation. High levels of inflammatory cytokines in the blood can lead to alterations in this electrocardiogram interval, as the inflammatory process stimulates the autonomic nervous system to release catecholamines. These catecholamines act directly on cardiac beta-1 receptors, causing tachyarrhythmias and QT interval prolongation. Additionally, these cytokines can alter the potential action of cardiomyocytes.[8] As a result, there is an observed increase in cardiac-related deaths among RA patients, since this QT interval alteration can lead to sudden death from tachyarrhythmia or ventricular fibrillation.

Given that this interval is affected by the presence of inflammatory cytokines, there may be a possible relationship between the ongoing inflammatory activity of the disease and QT interval prolongation. In the pursuit of better prognosis and treatment for RA patients—considering that their mortality is increased due to cardiac abnormalities—it is of utmost importance to conduct studies that confirm the correlation between Rheumatoid Arthritis and QT interval prolongation. Indeed, there are studies that suggest that the QT interval is influenced by serum PCR, as patients with QT prolongation had their intervals normalized once their PCR levels were reduced. Additionally, it was found that the prolongation is directly proportional to PCR values, meaning that the higher the number of circulating inflammatory cytokines, the longer the QT interval will be, since the decrease in PCR makes the QT interval less significant. [9] Thus, individuals affected by RA, who have chronic systemic inflammation, have a high chance of presenting QT prolongation, especially those without adequate rheumatological treatment; patients with higher PCR levels and consequently a longer QT interval are at greater risk of experiencing premature depolarizations, occurring before the completion of polarization, which can lead to severe ventricular arrhythmias that may progress to ventricular fibrillation and death [8,9].

In this work, the prevalence of QTc elongation in RA patients and its possible relation inflammatory activity was studied.

METHODS:

This is a cross-sectional observational study that used a convenience sample composed of individuals with RA treated at the Rheumatology outpatient clinic of the Mackenzie Evangelical University Hospital in Curitiba. Participants were selected according to their order of arrival for routine appointments, including those who consented to participate and who met the established inclusion and exclusion criteria.

This study was approved by the Research Ethics Committee of the Mackenzie Evangelical College of Paraná under protocol number 6.761.999. All participants signed informed consent forms.

The following data were collected: sex, age, disease duration, medications in use, presence of rheumatoid factor, and comorbidities. In addition, disease activity was measured using the DAS28-ESR (Disease Activity Score – using 28 joints and ESR), DAS28-CRP (using CRP), CDAI (Clinical Disease Activity Index), SDAI (Simplified Disease Activity Index), ESR and CRP values.

The DAS28 assesses the number of tender and swollen joints (based on 28 joints), ESR, CRP, and the patient's global assessment using a visual analog scale (VAS). Within the DAS scores: remission is considered when < 2.6; low disease activity when < 3.2; moderate disease activity when < 5.1; high disease activity when > 5.1. The

DAS28 formula is: 0.56 × √(tender joints) + 0.28 × √(swollen joints) + 0.70 × ln(ESR or CRP + 1) + 0.014 × VAS (patient).[10]

The CDAI is a purely clinical index, which does not require laboratory tests, making it a practical tool for real-time assessment of RA activity. It is calculated by summing the tender joint count, swollen joint count, patient global assessment, and physician global assessment, both using a 0–10 cm visual analog scale. Scores ≤ 2.8 indicate remission; between 2.9 and 10 = low activity; between 10.1 and 22 = moderate activity e 22 = high disease activity. [10]

The SDAI is similar to the CDAI but includes a laboratory marker of inflammation, CRP (mg/dL). Values ≤ 3.3 indicate remission; 3.4 to 11 = low activity; 11 to 26 = moderate activity; 26 = high activity. [10]

Next, patients underwent a 12-lead surface electrocardiogram, with a speed of 25 mm/sec and calibration (gain) of 10 mm/mV. The QT interval was corrected for heart rate using Bazett's formula. All readings were performed by a single researcher.

The QT interval was measured manually by the researchers using a magnifying glass, and Bazett's formula was then applied (QTc = measured QT / √RR, where "RR" is the interval between two consecutive R waves) to correct it for heart rate. We considered the following as normal QTc values: up to 0.450 seconds for women; up to 0.430 seconds for men, according to the American Heart Association (AHA) / American College of Cardiology (ACC) guidelines. QTc values were considered prolonged when > 0.450 s for men; > 0.460 s for women.[11,12.]

Inclusion criteria: - Included individuals were of both sexes, over 18 years of age, and met the ACR/EULAR criteria for RA classification.

Exclusion criteria: Excluded were individuals with known cardiac disease (e.g., myocarditis, pericarditis, coronary artery disease), other associated inflammatory diseases, use of antiarrhythmic drugs, or medications known to prolong the QTc interval (e.g., erythromycin, azithromycin, fluconazole).

Statistical analysis: Data were collected using frequency tables. Nominal data were expressed as percentages; numerical data were presented using central tendency measures: (median and interquartile range (IQR) when the sample was non-parametric; mean and standard deviation (SD) when the sample was parametric. Correlation studies between QTc interval and heart rate were performed using Spearman's test for non-parametric samples e Pearson's test for parametric samples. The significance level was set at 5% ($p < 0.05$). Calculations were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California, USA: www.graphpad.com

RESULTS:

A total of 97 individuals with RA were studied. The description of the studied sample can be found in Table 1. This table shows that the sample was predominantly composed of middle-aged to elderly women, reflecting the epidemiological profile of the disease. About 2/3 of the sample were rheumatoid factor positive, and the most common comorbidity was systemic arterial hypertension, followed by dyslipidemia. The most commonly used medications were leflunomide, methotrexate, and anti-TNF alpha.

Table 1 : Description of studied sample

Female sex -n		77.7%
Age – Years Median (IQR)		63.0 (55.5-68.5)
Disease duration - years – median (IQR)		11.0 (7.5-20.0)
Tobbaco exposure -n		39.5%
Positive rheumatoid fator -n		68.3%
Comorbidities s -n		
	Arterial hypertension	55.5%
	Diabetes mellitus	18.5%
	Hypothyroidism	23.4%
	Dyslipidemia	47.5%
Treatament -n		
	Methotrexat	40.7%
	Leflunomide	48.1%
	Anti TNF alfa	20.9%
	Tocilizumab	11.1%
	Rituximab	0
	Jak inhibitors	17.2%

N=number, IQR= interquartile range; Jak= janus quinases.

The disease activity data is found on Table 2. This table shows – through the measures of central tendency of disease activity – that most patients had their disease under control.

Table 2 – RA disease activity in the studied sample

	Range	Central tendency
ESR – mm – median (IQR)	2-120	22.5 (10-40)
C reative protein- median (IQR)	0-97	4.0 (0.88-8.50)
Hemoglobine – g/dL- median (IQR)	9.4 – 15.6	12.7 (12.0-13.9)
DAS-28 ESR – mean (SD)	0.77 - 5.10	2.77 (0.92)
DAS 28- CRP – median (IQR)	1.03- 5.95	2.04 (1.62-2.67)
CDAI – median (IQR)	0-41.0	3.0 (0.0-8.0)
SDAI – median (IQR)	0-39.0	3.4 (0.87-9.2)

ESR= sedimentation rate ; PCR= C reactive protein; DAS- disease activity score; CDAI – clinical disease activity index; SDAI= simplified disease activity index; IQR=interquartile range ; SD- standard deviation.

In this sample, the median heart rate was 70.0 bpm; IQR=64-79.0; the mean QTc interval was 410.0 s (IQR=387.5-437.0s). In this sample, there were 11/97 (11.3%) individuals with altered QTc. The study of the correlation between the QTc interval and heart rate with disease activity measures is in Table 3.

Table 3- Correlation studies of QTc interval and cardiac frequency with disease activity.

QTc interval	R	95%IC	P
ESR	0.12	- 0.11 a+ 0.36	0.29
C reative protein	-0.03	-0.26 a +0.19	0.75
Hemoglobine	-0.13	-0.35 a +0.09	0.24
DAS 28 ESR	0.04	-0.20 a + 0.28	0.73
DAS 28 CRP	0.007	-0.25 a +0.26	0.95
CDAI	-0.10	-0.33 a + 0.13	0.38
SDAI	-0.03	-0.29 a 0.22	0.76
Cardiac Frequency			
ESR	0.04	-0.18 a +0.22	0.70
C reative protein	0.15	-0.07 a +0.37	0.17
Hemoglobine	0.04	-0.18 a +0.27	0.68
DAS 28 ESR	0.09	-0.15 a + 0.32	0.46
DAS 28 CRP	0.17	-0.08 a + 0.41	0.16
CDAI	0.02	-0.21 a + 0.25	0.86
SDAI	0.14	-0.12 a +0.38	0.28

ESR= Sedimentation rate; CRP= C reactive protein; DAS- disease activity score; CDAI – clinical disease activity index; SDAI= simplified disease activity index; IQR= interquartile range; DP= standard deviation.

DISCUSSION

The study sample consisted of 97 patients, with more than two-thirds being middle-aged women—following the classic profile of patients with RA, and therefore representative of the disease under investigation. The results revealed a high number of individuals with prolonged QTc intervals, but it was not possible to associate this prolongation with the inflammatory activity of the disease.

These findings are in contrast to those of Adlan et al., who analyzed 112 patients with RA with an epidemiological profile similar to the present study—most of them women in their sixth decade of life. The patients underwent electrocardiograms and blood tests to assess inflammatory markers (including CRP, TNF-alpha, and interleukins), and the QTc interval was calculated using Bazett's formula. These authors obtained results

suggesting that a lower inflammatory burden may offer protection against QTc prolongation in patients with rheumatoid arthritis.

However, the study by Adlan et al. did not use clinical indices such as DAS28, CDAI, and SDAI to assess disease activity as was done in the present study. These are composite indices that consider pain and the patient's general health assessment, which may be influenced by non-inflammatory factors—potentially introducing bias in interpretation.[10] Moreover, it is important to note that the vast majority of patients in this study had relatively well-controlled disease, with no individuals presenting with high disease activity, limiting the ability to assess QTc prolongation in such cases.

One of the major causes of QTc interval prolongation is medication. Antimalarials—used as disease-modifying drugs—can affect the cardiovascular system and are most often associated with cardiotoxicity and atrioventricular blocks. Furthermore, these drugs have the potential to alter the QT interval on ECG. Although this possibility is described in the literature, albeit limitedly, it is often overlooked by the primary prescribers of these drugs, such as rheumatologists and infectious disease specialists.[13]

Chronic exposure to cytokines is known to modulate cardiac ion channels, reducing potassium outflow currents and increasing inward calcium and sodium currents, resulting in prolongation of the action potential and QT interval.[14] Kobayashi et al. conducted a comparative study between RA patients and a control group and found that QTc intervals were significantly longer in individuals with RA. The study provides direct evidence that inflammation control through interleukin-6 inhibition may reduce the risk of arrhythmias in these patients. They also demonstrated that variations in CRP levels independently predicted QTc changes, with this association being even stronger in patients who already had prolonged QTc at baseline.[15]

Interpreting the present findings, another possibility is that chronic exposure to pro-inflammatory cytokines causes subclinical myocardial toxicity, which in turn may lead to electrical conduction abnormalities in the heart. In this scenario, individuals with a history of uncontrolled inflammatory activity may have developed subclinical cardiomyopathy, which could explain the finding of QTc prolongation even when inflammatory activity is no longer present.[15]

This study is limited by its cross-sectional design and the small number of participants. Another limitation was the inclusion of mostly patients with low disease activity. However, given the high prevalence of QTc interval abnormalities found, this study clearly highlights the importance of monitoring cardiac function in patients with rheumatoid arthritis.

CONCLUSION

A significant prevalence of prolonged heart rate-corrected QT intervals (QTc) was observed in patients with rheumatoid arthritis (11.3%). In this sample, no correlation could be demonstrated between elevated QTc values on electrocardiogram and inflammatory disease activity.

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