QT and QT dispersion intervals in long-standing and moderately active rheumatoid arthritis: results from a multicentre cross-sectional study

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Abstract

Objective

To define the prevalence of prolonged QT interval and QT dispersion (QTd) in rheumatoid arthritis (RA) patients and in a control population.

Methods

QT interval corrected by Bazett's formula (QTc) was calculated from standard 12-lead ECGs in 963 subjects free of previous cardiovascular events (646 RA patients and 317 controls strictly matched for age, sex and cardiovascular risk factors).

Results

RA patients (59.6±9.6 years, 68.1% females) had a long mean disease duration (10.6 years) and moderate disease activity (DAS28=3.68±1.23). QTc was 5 msec longer in RA patients than in controls (412±9 vs. 407±28 msec, p=0.013). However, the prevalence of QTc prolongation in RA patients and controls was not significantly different (5.3% vs. 6.3%, p=0.50). On the contrary, RA patients had a significantly greater QTd (42±26 vs. 35±18 msec, p<0.001) and a higher prevalence of increased QTd (33.3% vs. 18.3%, p<0.001) than controls. Furthermore, RA was independently associated to increased QTd [OR(95%CI)= 2.21(1.58–3.08), p=0.0001]. In the RA population, male gender and older age were independently associated with a higher prevalence of prolonged QTd.

Conclusion

In this cohort of long-standing and moderately active RA patients, RA showed longer QTc but similar prevalence of prolonged QTc and an increased QTd with a 1.8-fold higher prevalence of increased QTd than the control population. Further studies in larger prospective cohorts are warranted to investigate whether QTd prolongation predicts sudden cardiac death and other adverse cardiovascular outcomes in RA.

Key words

rheumatoid arthritis, QT dispersion, QT prolongation, arrhythmias, electrocardiography

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Introduction

Rheumatoid arthritis (RA), an autoimmune disease that affects 1% of the general population, is characterised by chronic joint damage, systemic inflammation, and excess of mortality, particularly cardiovascular mortality (1). Despite improved survival in recent years, due to early diagnosis and effective treatment, the impact of atherosclerotic cardiovascular disease remains high in RA patients (2, 3). This is primarily due to accelerated endothelial dysfunction, arterial stiffening and premature atherosclerosis (4-8). Furthermore, RA is associated with a nearly two-fold increase in the risk of sudden cardiac death and cardiac arrest compared to the general population. This risk appears to be largely independent of conventional risk factors (9). Prolonged heart rate (HR)-corrected QT (QTc) interval and QT dispersion (QTd), measures of abnormal repolarisation, have been linked to increased arrhythmogenic potential and risk of sudden cardiac death in the general population (10-12). Recently, a high prevalence of prolonged QTc interval and QTd has been reported in patients with diabetes (13, 14), a condition sharing with RA a similar profile of cardiovascular risk15. However, there is limited information on whether RA *per se* is independently associated with prolonged QT and QTd.

We sought to address this issue by investigating the prevalence and the determinants of prolonged QT interval and QTd in a large population of RA patients, free from previous cardiovascular events, and in an age- and sex-matched control group with a similar prevalence of cardiovascular risk factors.

Methods

Patients and controls

We collected data on QTc interval and QTd in a consecutive series of RA patients aged 45–85 years, free from previous cardiovascular events, prospectively enrolled in the Endothelial Dysfunction Evaluation for Coronary Heart Disease Risk Estimation in Rheumatoid Arthritis study (the EDRA study, ClinicalTrials.gov: NCT02341066) (5) between October 2015 and July 2017. The EDRA study is a multicentre 3-year prospective cohort study with three participating Rheumatology Units (Sassari, Cagliari and Rome, Italy), investigating the incremental value of peripheral endothelial dysfunction, when added to the Framingham risk score, in predicting future coronary events. Inclusion criteria were: a) Men and women aged >45 and <85 years; b) RA defined by ACR/EULAR 2010 RA classification criteria (16).

Controls matched for age, gender and cardiovascular risk factors (diabetes, hypertension, dyslipidaemia, and smoking) were enrolled from subjects referred to the cardiology outpatient's clinic of the Azienda Ospedaliero-Universitaria of Sassari (Italy) for a screening visit.

Clinical exclusion criteria for RA patients and controls were: a) previous cardiovascular or cerebrovascular events (acute coronary syndrome, stable angina, stroke, interventional procedures, carotid endarterectomy, symptomatic peripheral artery ischaemia); b) serious infections in the previous 6 months; c) concomitant severe illness (overt hepatic and/or renal disease, glomerular filtration rate <30 ml/min, calculated by the Cockcroft-Gault formula); d) recent diagnosis of cancer; e) pregnancy.

Additional exclusion criteria were the presence of any of the following ECG abnormalities: a) Left or right bundle branch block; b) Atrial fibrillation; c) Evidence of previous myocardial infarction (pathological Q-waves and associated repolarisation abnormalities).

We also excluded RA patients and controls taking drugs associated with an increased risk of QT interval prolongation such as class I and III antiarrhythmics, digitalis and antidepressants (17).

The EDRA study was approved by the Ethics Committee of Azienda ASL 1 of Sassari (Italy) (2126/CE-2015) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject before the study.

Clinical assessment

As per protocol, RA patients underwent a cardiologic evaluation, that included physical examination and ECG recording, in order to assess the presence of current or previous cardiovas-

cular disease or risk factors. Controls attending a screening program for cardiovascular diseases were asked to participate in the study once previous or current cardiovascular disease has been ruled out. Hypertension, diabetes, and dyslipidaemia were defined on the basis of self-reported diagnosis, use of disease-specific drugs and, when available, laboratory data.

In RA patients, the following disease specific scores, disease descriptors, and treatment data were collected on the same day of the ECG recording: steroid treatment; cumulative steroid dose in the last month; treatment with synthetic or biological disease-modifying antirheumatic drugs (DMARDs); number of swollen joints; number of tender joints; C-reactive protein (CRP) concentrations; erythrocyte sedimentation rate (ESR); Disease Activity Score-28 (DAS-28); Health Assessment Questionnaire (HAQ); positivity for rheumatoid factor (RF) and anti-citrullinated cyclic peptide antibodies (ACPA).

In a subgroup of 390 subjects (236 controls and 154 RA patients), data on serum potassium (K) and calcium (Ca) concentrations, measured on the same day of the ECG recording, were also available: hypokalaemia was defined as serum K<3.5 mEq/L, and hypocalcaemia as serum calcium Ca <8.9 mg/dl.

ECG variables

The QT interval was manually measured on 12-lead ECGs, from the onset of the QRS complex to the end of the T wave, defined as the return to the T-P baseline. When U waves were present, the QT interval was measured at the nadir of the curve between the T and U waves. When prominent U waves (>1 mm) merging into T waves were present, they were included in the QT measurement (18). QT was measured in lead II. When QT interval was not clearly identified in lead II (*e.g.* due to low voltage complex), leads V5 or V6 were used (19). Heart rate correction (QTc) was performed using the Bazett's formula ($QTc = QT/\sqrt{RR}$) (20). According to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines (19), QTc interval was considered prolonged if ≥450 msec in males or ≥460 msec in females. Marked QTc prolongation was identified when the QTc interval was >500 msec.

QT dispersion was defined as the difference between the minimum and maximum QT interval among the 12 ECG leads: a QTd >60 msec was considered as prolonged (21).

All ECGs tracings were centralised and assessed by a senior cardiologist that was blinded for the diagnosis of RA (PSS).

Patient and public involvement

This research was done without patient involvement. The patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results, nor were they invited to contribute to the writing or editing of this document for readability or accuracy.

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequencies (n) and percentages (%). Comparisons of means across groups were assessed by *t*-test and proportions by chi-square statistics. Variables associated to prolonged QT intervals with a $p<0.05$ and variables considered biologically plausible were entered into multiple logistic regression models in which the presence of prolonged QT interval was the variable to be explained. Models were adjusted for age (10-year increments), gender and cardiovascular risk factors. Results are expressed as odds ratio (OR) and 95% confidence interval (95% CI).

Analyses were performed using STATA14 (Stata Corp LP, 4095 Lakeway Drive, College Station (TX), 77845 USA). Graphs were made using GraphPad Prism 7 (GraphPad Software 7825, Fay Avenue, Suite 230, La Jolla (CA), 92037 USA).

A $p<0.05$ was considered statistically significant.

Table I. Demographic features and cardiovascular risk factors of RA patients and controls.

	Controls n=317	RA n=646	*p*-value
Age	59.6 ± 9.6	60.7 ± 9.4	0.10
Female, n (%)	216 (68.1)	453 (70.1)	0.53
Hypertension , n (%)	103 (32.5)	236 (36.5)	0.21
Dyslipidaemia, n (%)	108 (34.1)	204 (31.6)	0.43
Diabetes, n (%)	29 (9.1)	47 (7.3)	0.31
Current smoker, n (%)	60 (18.9)	134 (20.7)	0.50
Serum potassium, mEq/L*	4.3 ± 0.5	4.2 ± 0.4	0.03
Serum calcium, mg/dl*	9.2 ± 0.5	9.2 ± 0.4	0.98
Hypokalaemia, n (%)*	12 (5.1)	10 (6.5)	0.55
Hypocalcaemia, n (%)*	33 (14)	19 (12.8)	0.71

Values are mean ± SD. RA: rheumatoid arthritis. *Data available in 236 Controls and 154 RA patients.

Results

Patients and controls

A total of 317 controls and 646 RA patients were studied. Age, gender distribution, and prevalence of cardiovascular risk factors were similar across groups by matching as per protocol (Table I). As expected, according to disease epidemiology, the female gender was the prevalent one.

Even if in the normal range, potassium concentrations were slightly lower in RA patients. However, the prevalence of hypokalaemia was not significantly different between groups. No difference in calcium concentrations was observed across groups.

RA patients had a relatively long mean disease duration (10.6 years), moderate mean disease activity (DAS28=3.68) and were mostly (97%) under immunosuppressive and anti-inflammatory treatment at the time of ECG recording (Table II).

ECG variables

Heart rate was slightly but significantly lower in RA patients than controls. QTc was significantly longer in RA *vs*. controls (412±29 *vs*. 407±28 msec, $p=0.01$). However, the prevalence of prolonged QTc in RA patients was not

Table II. Clinical and laboratory features of RA patients.

	RA, n=646
Disease duration, months	127.5 ± 114.5
RF, %	69.5
ACPA, %	61.1
ESR, mm/h	27.3 ± 21.9
CRP, mg/dL	1.87 ± 5.7
DAS-28	3.68 ± 1.3
HAQ (0-3)	0.77 ± 0.6
Steroids use, %	39.6
Steroids dose, mg/day	2.35 ± 8
Steroids cumulative dose, mg/month	70.6 ± 245
NSAIDs use, %	23.2
DMARDs use, %	76.2
TNF-inhibitors use, %	26
Abatacept use, %	4.5
Tocilizumab use, %	7
Rituximab use, %	2.5
Treatment-naive, %	3

Values are mean ± SD. ACPA: anti citrullinated cyclic peptide antibodies; CRP: C-reactive protein; DAS-28. Disease Activity Score-28; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; NSAIDs: non-steroidal anti-inflammatory drugs; RF: rheumatoid factor; TNF-inhibitors: tumour necrosis factor alpha-inhibitors.

significantly different from controls (5.3% *vs*. 6.3%, p=0.50). Similarly, the prevalence of marked QTc prolongation was similar between the two groups. QTd was significantly longer in RA patients than in controls (42±26 *vs*. 35±18 msec, p<0.001). Moreover, RA patients had a significantly higher prevalence of prolonged QTd (33.3% *vs*. 18.3%, p<0.001) than controls. (Table III).

Consistent results were obtained in the sample with electrolytes (Supplementary Table S1), with RA patients showing longer QTc (418±30 *vs*. 408±29 msec, p<0.001) but similar prevalence of prolonged QTc (9.7% *vs*. 7.2%, p=0.37), and increased QTd (48±25 *vs*. 38±16 msec, p<0.001) with higher prevalence of prolonged QTd (40.9% *vs*. 21.6%, p<0.001) than their control counterpart.

Risk factors for QTd prolongation

• Overall sample (n=963) (Fig. 1A).

In multiple logistic regression analyses RA was independently associated with the presence of prolonged QTd [OR(95%CI) = 2.15(1.35–3.02), p<0.001] after adjusting for age, heart rate and cardiovascular risk factors. Besides RA, older age and male gender were also independently associated with prolonged QTd while dyslipidaemia was inversely associated with prolonged QTd.

• RA sample (n=646) (Fig. 1B)

Increasing age and male gender were independently associated to increased prevalence of prolonged QTd in the RA sample. Similar to what observed in the overall sample, dyslipidaemia was inversely associated with prolonged QTd. No significant associations between other RA-specific variables (such as disease duration, CRP concentrations, ESR, ACPA positivity, RF positivity and type of immunosuppressive treatment) and the presence of prolonged QTd were observed (Suppl. Table S2).

• Subgroup with electrolytes (n=390) (Fig. 1C)

In the subgroup of subjects with available electrolytes, RA remained significantly associated with prolonged QTd. As above, the presence of dyslipidaemia was associated with reduced risk of QTd prolongation.

Discussion

In this large cross-sectional case-control study we reported similar prevalence of prolonged QTc interval in RA patients in comparison to the general population, although mean QTc values in patients were significantly higher than controls. This first finding is consistent with the results of a recent retrospective population-based cross-sectional study by Chauhan *et al*., which similarly failed to show increased QTc prolongation in RA with respect to the general population (22); In this study, only "cumulative incidence" of QTc prolongation (at 20 years of follow-up after the date of RA incidence) was significantly increased in RA patients in comparison to non-RA subjects, also associating with erythrocyte sedimentation rate (ESR) at the time of diagnosis (22).

Indeed, ESR, C-reactive protein (expression of local and systemic inflammatory burden in RA) and interleukin-6 (IL-6) are thought to be risk factors for QTc and QTd prolongation, as well as malignant ventricular arrhythmias, in the RA population (23, 24). From an experimental and mechanistic point of view, pro-inflammatory cytokines are proven to induce changes in potassium and calcium channels, leading to the prolongation of the cardiomyocyte action potential (25). Moreover, it has been shown that in RA patients the risk of atrial fibrillation is increased by 30% compared to the general population (26) and in an animal model of RA, both AF vulnerability and atrial remodelling have been associated with proinflammatory cytokines (27).

The lack of association between RA and prolonged QTc observed in our study might be related to the characteristics of our study population, which included RA patients chronically treated with immunosuppressive and anti-inflammatory drugs, moderate mean disease activity (mean DAS-28=3.6) and relatively low mean CRP and ESR values (28). Thus, it can be speculated that in our cohort inflammatory cytokine levels are not high enough to induce evident QTc prolongation, also suggesting that long-lasting, albeit partial disease control may be already sufficient to reduce ventricular arrhythmic risk in RA. In addition, our data indirectly support previous studies suggesting that QTc prolongation in these patients is mainly

Table III. ECG parameters.

	Controls, n=317	RA, n=646	p-value
Heart rate, bpm	73 ± 13	69 ± 10	<0.001
QTcBAZ, msec	407 ± 28	412 ± 29	0.01
Prolonged QTc, %	20 (6.3)	34 (5.3)	0.50
Marked QTc prolongation, n(%)	5 (1.6)	12 (1.9)	0.75
QTd, msec	35 ± 18	42 ± 26	<0.001
Prolonged QTd, n(%)	58 (18.3)	215 (33.3)	<0.001

Values are mean ± SD. Bpm: beat per minute; Marked QTc prolongation: QTc ≥ 500 msec; msec: milliseconds; Prolonged QTc: QTC ≥450 msec in males and ≥460 msec in females; QTcBAZ: QT interval corrected for the heart rate by Bazett's formula; Prolonged QTd, QTd ≥60 msec.

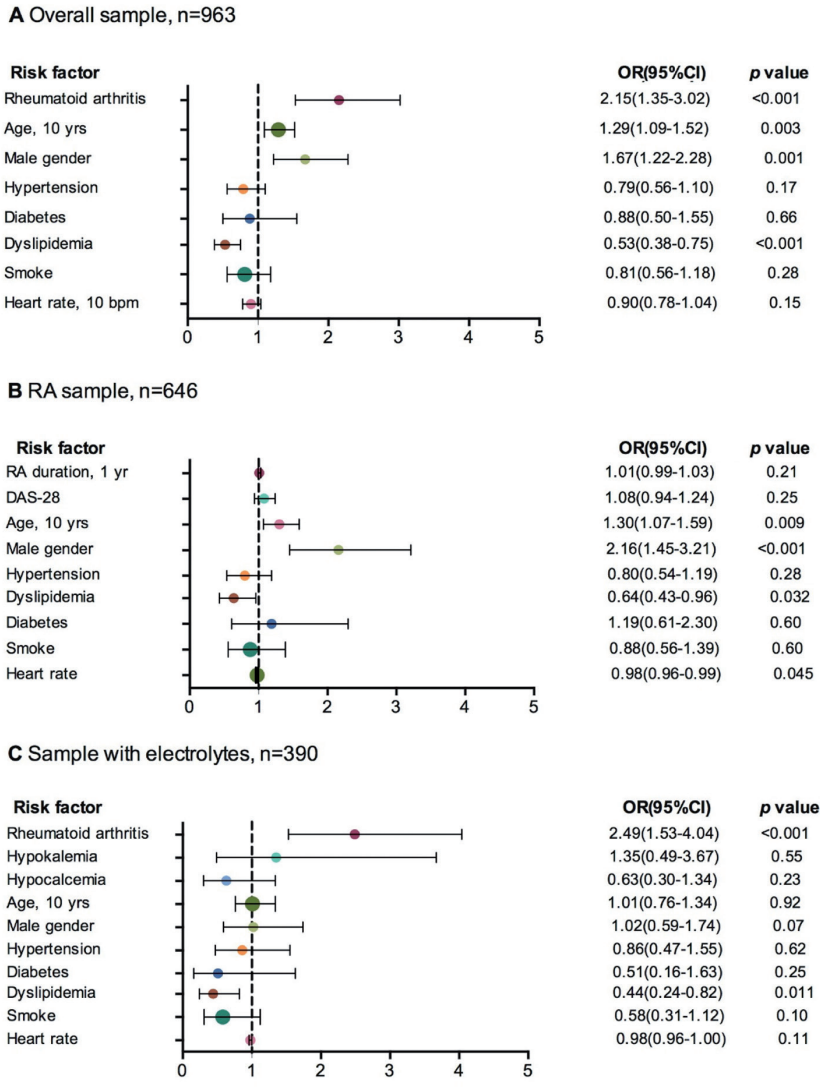

Fig. 1. Risk factors for prolonged QTd.
Forrest plots represent adjusted odds ratios (OR) with 95% confidence interval (95%CI) calculated with multiple logistic analyses (ENTER method). The models included variables considered biologically plausible and variables showing significant ($p<0.05$) association with the dependent variable in binary logistic analysis adjusting for sex, age, heart rate (HR) and cardiovascular risk factors.

present during flares of high-grade systemic inflammation (23, 24, 29), due to direct and reversible electrophysiological effects of cytokines, rather than the result of chronic inflammatory-driven structural alterations of the heart.

On the other hand, the evidence of a longer mean QTc in patients in comparison to controls points anyway to an impact of residual inflammatory activation on ventricular repolarisation duration.

As a result, we cannot exclude that the prospective evaluation of our cohort will allow to identify a tangible increase in the cumulative incidence of prolonged QTc in RA, as reported by Chauhan *et al*. (22). In fact, although comprised within normal values, the longer mean QTc duration observed in RA *versus* controls may indicate a reduced repolarisation reserve in these patients, thus potentially suggesting an increased susceptibility to develop QTc prolongation (and related life-threatening arrhythmias) when other intercurrent QT-prolonging factor occur, such as drugs, electrolyte imbalances, acute cardiac events.

QTd, originally proposed as an index of spatial dispersion of the ventricular recovery (30), is now considered an indirect measure of general repolarisation abnormalities (21). In two large prospective studies prolonged QTd was associated with a significant increase in the risk of future cardiovascular events (11, 31).

In our series, using a cut-off of 60 msec, we recorded a prolonged QTd in one third of RA patients, corresponding to a 1.8-fold higher prevalence in this group compared to the control population. This result confirms the findings from five smaller studies (mean sample size of 54 RA patients) reporting significant prolongation of QTd in RA patients in comparison with the general population (32-35). In these studies, QTd prolongation appeared to be variably associated to longer (32, 35), more severe (33, 34), and extra-articular disease (32, 34). Conversely, in our series of RA patients, apart from associations with age, male sex and absence of dyslipidaemia, we did not identify any RA-specific features that were significantly associated with prolonged QTd.

The increased prevalence of prolonged QTd in the RA population in our study might reflect repolarisation abnormalities, as suggested in the general population (21). This hypothesis is supported by the results of a population-based cohort study showing a significantly increased cumulative incidence of ST-T wave changes in RA patients with respect to the general population (RA: 33% *vs*. non-RA: 21%) (22).

Regardless of the pathophysiological background, the higher prevalence of prolonged QTd (and repolarisation abnormalities) may contribute to the increased risk of arrhythmogenic cardiovascular events and sudden death in the RA population. In any case, our data point to QTd as a more sensitive parameter than QTc in reflecting ventricular repolarisation abnormalities in RA patients with not highly active disease.

In our study, the presence of dyslipidaemia was a significant protective factor for prolonged QTd, both in the whole sample and in the RA subgroup. These results are of interest and need further confirmation, considering that dyslipidaemia is not included among known acquired factors that predispose to pro-

longed QTd and higher risk of torsades de pointes in the general population (36).

However, some epidemiological studies provided strong evidence for an inverse relationship between omega-3 polyunsaturated fatty acids and cardiac mortality, possibly based on pro-arrhythmic effects of omega-3 polyunsaturated fatty acids on ion channels and calcium regulatory proteins (37). It was also proposed that hypercholesterolaemia may be protective against ischaemia induced arrhythmias (38). Moreover, it should be considered that the increased cardiovascular risk observed in RA population has been shown to be paradoxically associated with low total cholesterol concentrations, an inflammation-related pattern known as the "lipid paradox" (39).

Our study has some potential limitations. First, the vast majority of RA patients were under treatment with immunosuppressive and anti-inflammatory drugs at the time of enrollment; However, it should be acknowledged that the impact of new biological therapies on cardiac repolarisation, variability and arrhythmogenic potential is not currently clear since both anti and pro-arrhythmic effects were reported (40-42). In addition, considering the absence of any association in logistic regression analysis, in our series of RA patients the treatment regimen appeared to have no significant effect on QT measures.

Second, electrolyte data were available only in a subgroup of subjects: however, even in this subgroup, the logistic analysis confirmed the independent association between RA and prolonged QTd.

Third, data on echocardiographic parameters (in particular left ventricular mass) were not available in this study population, and therefore we were not able to investigate possible associations between cardiac structural modifications and QT intervals.

Conclusions

RA patients with long disease duration and moderate disease activity do not have an increased prevalence of prolonged QTc when compared to a general population with a similar prevalence of cardiovascular risk factors. On the contrary, RA patients had a significantly higher prevalence of QTd prolongation. Our data suggest that although long-lasting maintenance of moderate disease activity may be already sufficient to reduce ventricular arrhythmic risk in RA, a residual risk could be still present more sensitively reflected by QTd.

Further studies in larger prospective cohorts are warranted to investigate whether QTd prolongation, regardless of its pathophysiological mechanisms, predicts sudden cardiac death and other adverse cardiovascular outcomes in the RA population.

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