J R Coll Physicians Edinb 2020; 50: 380–6 | doi: 10.4997/JRCPE.2020.406 ORIGINAL RESEARCH PAPER

QT interval parameters, anti-Ro antibody status, and disease activity in systemic lupus erythematosus

Mohamed Azharudeen[1], Molly Mary Thabah[2], Santhosh Satheesh[3], Vir Singh Negi[4]

Abstract

Background: The QT interval a marker of ventricular depolarization and repolarization is reported to be prolonged in some proportion of patients with systemic lupus erythematosus (SLE). We studied electrocardiographic (ECG) abnormalities, in particular QT interval and its relationship with anti-Ro antibodies, disease activity, and serum interleukin 1β (IL-1β), interleukin 6 (IL-6) in SLE.

Methods: A 12-lead resting ECG was performed on 140 adult SLE patients fulfilling SLICC/ACR classification criteria. All patients received hydroxychloroquine and prednisolone. Corrected QT (QTc) ≥440 milliseconds (ms) was defined as prolonged QTc. QT dispersion (QTd) ≥60 ms was defined as increased QTd.

Results: Eighty-four patients had some form of ECG abnormality. Prolongation of QTc and QTd was present in 24 (17.1%) and 50 (35.7%) respectively. Anti-Ro/SSA antibodies were present in 63 (45%). Prolongation of QTc in anti-Ro positive versus anti-Ro negative was 17.5% and 17% respectively, p=0.98. Prolongation of QTd in anti-Ro-positive versus anti-Ro-negative was 32% and 39% respectively, p=0.37. Prolonged QTc was observed in 15% patients with SLEDAI ≤4 compared to 17.5% patients with SLEDAI ≥5, p=0.78. The median serum concentrations of IL-1β and IL-6 were similar in the groups with and without prolonged QTc, with and without prolonged QTd. On binary logistic regression analyses neither clinical nor laboratory factors were predictors of prolonged QTc. However, having valvular regurgitation and hypercholesterolemia was associated with significantly reduced odds of having prolonged QTd, adjusted OR 0.33 (CI 0.14-0.83), p=0.018 and 0.19 (CI 0.05-0.80), p=0.023 respectively. Those with high LDL cholesterol and hypertriglyceridemia had a significantly higher odds of having a normal QTd with adjusted OR of 4.34 (1.31-14.46) p=0.017and 5.59 (1.62-19.38) p=0.007respectively.

Conclusion: Though 17% and 35% SLE patients have QTc and QTd prolongation, association with anti-Ro antibodies or disease activity was absent. A large proportion has other asymptomatic ECG abnormalities that may reflect subclinical cardiac involvement.

Keywords: lupus, QT interval, QT dispersion, interleukin 1β, interleukin 6

Correspondence to:
Molly Mary Thabah
Department of Medicine
Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER)
Puducherry
India 605006

Email:
thabah.m@jipmer.edu.in
mollymthabah@gmail.com

Introduction

Systemic lupus erythematosus (SLE) or lupus is the prototype multisystem autoimmune disease characterized by the production of multiple autoantibodies. Cardiovascular (CV) involvement in SLE occurs in the form of pericarditis, myocarditis, endocardial involvement,[1,2] and premature atherosclerosis.[3,4] There are reports that SLE patients have ventricular repolarization abnormalities related to anti-Ro antibodies.[5] These investigations were initiated because of the well-known association that 2% of babies born to anti-Ro positive mothers develop congenital complete heart block in utero.[6] The QT interval that is measured in a surface electrocardiogram (ECG) from beginning of QRS to the end of T wave, is a measure of overall ventricular depolarization and repolarization.[7] The difference between the maximum and minimum corrected QT (QTc) interval is called QT dispersion (QTd).[7] Prolonged QTc and QTd indicate abnormal ventricular repolarization linked to development of arrhythmia.[8] In the general population prolonged QTc and QTd are linked to development of coronary heart disease, increased CV-related mortality,[9] and are a predictor of mortality in the elderly.[10]

[1]Junior Resident, Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry, India; [2]Additional Professor, Department of Medicine, JIPMER, Puducherry, India; [3]Professor, Department of Cardiology, JIPMER, Puducherry, India; [4]Senior Professor and Head, Department of Clinical Immunology, JIPMER, Puducherry, India

A study from India reported that 51% of newly diagnosed, hydroxychloroquine (HCQ) naïve SLE patients had prolonged QTc, that was significantly higher during a flare as compared to baseline.[11] A study from the SLE collaborating clinics (SLICC) cohort showed that 15.3% lupus patients had prolonged QTc but no association with disease activity was found.[12] Limited data therefore suggests that prolongation of QT interval has important clinical implications in SLE as a probable marker of active disease, and a predisposition to the occurrence of cardiac arrhythmias.

The primary objective of our study was therefore to assess the electrocardiographic (ECG) findings in SLE for prevalence of prolonged QTc and QTd. We also assessed the associations of ventricular repolarization abnormalities (prolonged QTc & QTd) with anti-Ro antibodies, disease activity, and serum interleukins.

Methods

Patients; We performed a prospective observational study from 1 December 2017 until 31 March 2019. Adult SLE patients fulfilling the SLE International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) 2012 classification criteria were eligible for inclusion. Those with overlap syndromes were excluded. Demographic and clinical variables, namely mucocutaneous, musculoskeletal, haematological manifestations, lupus nephritis, neuropsychiatric lupus or other organ involvement were recorded. Disease activity was assessed by the SLE disease activity index 2000 (SLEDAI-2K).[13] Current medication namely prednisolone, HCQ, and medications that could affect QT interval (such as amitriptyline) were collected from case records and by patient interview. Serum potassium, serum calcium, and serum magnesium estimation was obtained to rule out hypokalaemia, hypocalcemia, hypomagnesemia respectively, as electrolyte imbalance is known to produce abnormal findings on the ECG. Cardiovascular disease (CVD) risk factors namely blood pressure, body mass index (BMI) in Kg/m2, lipid profile and fasting blood glucose were also measured.

Assessments

ECG Recording

A 12 lead ECG was recorded at 25 mm/second paper speed and 10 mm/mV amplitude, using ECG machine located in the cardiology outpatient unit. Before an ECG recording the patient should have rested for at least 10 minutes. ECG findings and interpretation were made (by author MAA) and confirmed by a cardiologist (SS) who was blinded to the patient's clinical status. QT interval was measured from beginning of QRS to end of T-wave. The QT was measured in multiple leads and the longest QT interval in the whole 12-lead ECG recording was taken as QT interval.[14,15] QTc is the QT interval corrected for the heart rate, and was calculated by Bazett formula which is $QTc = QT/\sqrt{RR}$.[14,15] The normal values of QTc ranges from 330 milliseconds (ms) to 440ms. Prolonged QTc was defined as QTc ≥440ms, as has been earlier reported.[5,11,12] QT dispersion (QTd) defined as the difference between maximum and minimum non-corrected QT-interval duration, usually has a range from 10 to 70 ms. In this study we defined increased QTd as >60 ms as is widely accepted.[7,16] Other ECG findings namely PR interval, non-specific ST-T changes, left ventricular hypertrophy, left atrial enlargement, left bundle branch block, and right bundle branch block were defined using standard definitions.[14] A transthoracic 2D ECG was done to look for pericardial effusion, valvular regurgitations, left ventricular function, and right ventricular systolic pressure.

Laboratory investigations

Separated sera were stored at -80 degrees until analysis. Anti-Ro/SSA, anti-LA/SSB were tested using a 17-antigen semi quantitative line immunoassay. Serum interleukin-1β (IL-1β) and interleukin 6 (IL-6) were measured by enzyme-linked immunosorbent assay (ELISA) using commercial ELISA kits. Serum complements (C3 and C4), and hsCRP were measured by nephelometer.

Statistical Analysis

Sample size (n=140) was estimated with an expected percentage of SLE patients with ECG abnormality with reference to QTc as 51%.[11] The sample size was estimated with 5% level of significance and 15% relative precision.

For analyses, descriptive statistics was used. Comparison of categorical variables was carried out using Chi square test or Fisher's exact test. Median QTc, QTd between anti-Ro positive and anti-Ro negative, median hsCRP, C3, C4, SLEDAI score, IL-1β, IL-6 between those having prolonged versus normal QTc were compared using Mann-Whitney U-test. Multivariable binary logistic regression was performed by including all variables in the unadjusted analysis, and adjusted odds ratio (AOR) with 95% CI was calculated. All statistical analysis was carried out at 5% level of significance and p-value <0.05 was considered significant. Data was analysed using IBM SPSS Statistics for Windows, version 21.

Ethical approval

All patients gave written informed consent before participating in the study. The study protocol was approved by the institute ethics committee vide letter Ref. No: JIP/IEC/2017/0313.

Results

Of 140 patients, 120 (85.7%) had disease duration <2 years. The median SLEDAI was 12 (IQR 8-16), 120 (85.7%) had active disease (SLEDAI ≥4), and 20 (14.28%) had inactive/low disease activity (SLEDAI <4). The baseline clinical characteristics are summarized in Table 1. Anti-dsDNA was positive in 69 (49.3%), anti-Sm 55 (39.3%), 63 (45%) were positive for anti-Ro/SSA and anti-La/SSB was positive in 34 (24.3%). All patients were receiving HCQ and prednisolone. Only 5 patients were on low dose amitriptyline, none of whom had QT prolongation. None were on other medications that are known to prolong QTc. Five patients had hypokalaemia, of whom two had QT prolongation. In these two patients hypokalaemia was corrected, and repeat

Table 1 Baseline clinical characteristics of the patients with SLE

Clinical Manifestations	n=140
Age in years, mean± SD	28.7 ±9.5
Duration of disease (months), median (IQR)	8 (5-13.5)
Women, n (%)	131 (93.5)
Mucocutaneous manifestations, n (%)	96 (68.6)
Arthritis or arthralgia, n (%)	60 (42.9)
Serositis, n (%)	18 (12.3)
Thrombocytopenia (platelet count <100,000/mm^3), n (%)	20 (13.4)
Leukopenia (total leukocyte count < 4000/mm^3), n (%)	15 (10.1)
Autoimmune haemolytic anaemia, n (%)	13 (9)
Lupus nephritis, n (%)	49 (35)
Neuropsychiatric lupus, n (%)	8 (5.7)
Myositis, n (%)	8 (5.7)
Vasculitis, n (%)	19 (13.6)
Hydroxychloroquine, n (%)	140 (100)
Echocardiographic findings	
Left ventricular ejection fraction <50%, n (%)	11 (7.9)
Pericardial effusion, n (%)	18 (12.8)
Valvular regurgitation, n (%)	48 (34.3)
Right ventricular systolic pressure ≥40mmHg, n (%)	6 (4.2)

Table 2 Electrocardiographic (ECG) findings in SLE patients

ECG variables	n= 140
Rate, median (IQR)	89 (76-102)
Tachycardia (rate >100/minute), n (%)	40 (28.6)
QTc in ms, median (IQR)	400 (380-420)
Prolonged QTc (QTc>440 ms), n (%)	24 (17.1)
QTd in ms, median (IQR)	40 (40-80)
Increased QTd (>60 ms), n (%)	50 (35.7)
PR interval in ms, median (IQR)	120 (120-160)
PR interval prolongation, n (%)	0
Left ventricular hypertrophy, n (%)	6 (4.3)
Right ventricular hypertrophy, n (%)	0
Left bundle branch block (LBBB), n (%)	1 ((0.7)
Right bundle branch block (RBBB), n (%)	1 (0.7)
Left anterior fascicular block & left posterior fascicular block, n (%)	0
Non-specific ST-T changes (T inversion, ST segment depressions), n (%)	11 (7.5)
Supraventricular arrhythmias, n (%)	0
Ventricular premature contractions (VPCs), n (%)	5 (3.5)

QTc: corrected QT interval; QTd: QT dispersion; ms: milliseconds; PR: PR interval

ECG recording showed a normal duration of QT. Twelve had hypocalcemia, six had hypomagnesemia. For all these patients the electrolyte abnormalities were corrected, and ECG was taken again.

CVD risk factors

Six patient had diabetes, of whom one had diabetes before onset of disease, and five had developed diabetes during their course of illness; 39 were hypertensive, and 49 were obese (BMI >25).[17] Sixty-nine (49.3%) had low HDL (HDL cholesterol <40 mg/dL in men, <50 mg/dL in women), and 44 (31%) had LDL cholesterol >100 mg/dL.

ECG findings

Overall, 84 patients (60%) had some form of ECG abnormality, of which the most common was sinus tachycardia (Table 2). Eleven patients had non-specific ST-T changes, none of these patients had angina. Two patients with ST depression had hypokalaemia. None of the ECG findings noted here (i.e. ST-T changes, ST depression) were consistent with myocardial ischemia.

QT interval parameters and anti-Ro antibodies

Twenty-four (17.1%) had QTc ≥440 ms, 50 (35.7%) patients had QTd >60ms. The proportion of patients having prolonged QTc was 17.5% and 16.9% in the anti-Ro positive and anti-Ro negative group respectively (Table 3). Since in general population prolonged QTc in women is defined as QTc >460ms we performed subgroup analysis of QTc and QTd among women, but there was no statistical significance (Table 3). Similarly, the proportion of patients with increased QTd was not significantly different between anti-Ro positive and anti-Ro negative patients.

IL-1β and IL-6, disease activity, clinical features and QT interval parameters

Serum IL-1β, IL-6 were comparable in those with and without prolonged QTc/QTd (Table 4). Likewise, hsCRP, complements, and SLEDAI were comparable in the groups. On univariate analysis there was no association of disease duration, disease activity, clinical manifestations, ECG findings or CVD risk factors with either QTc nor QTd prolongation, except for mucocutanoeus manifestations (supplementary table).

A binary logistic regression analyses was performed by including all variables in the unadjusted analysis, except for those variables that had a count of <5 in each cell namely neuropsychiatric lupus, haematological manifestations, poor left ventricular ejection fraction and diabetes. As shown in

Table 3 Association of QTc and QTd with anti-Ro antibodies

ECG Parameter	Anti-Ro Positive n=63, n (%)	Anti-Ro Negative n=77, n (%)	p
QTc >440 ms (n=24)	11 (17.5)	13 (16.9)	0.98
QTc >460 ms (n=14)	6 (9.5)	8 (10.4)	1
QTd >60 ms (n=50)	20 (31.7)	30 (39)	0.37
QTc ms, median (IQR)	400 (380-420)	400 (380-415)	0.364
QTd ms, median (IQR)	40 (40-80)	40 (40-80)	0.124
Association of QTc and QTd with anti-Ro antibodies among women, n=131			
ECG Parameter	**Anti-Ro Positive n=60, n (%)**	**Anti-Ro Negative n=71, n (%)**	**p**
QTc >440 ms (N=20)	9 (15)	11 (15.5)	1
QTc >460 ms (n=10)	4 (6.7)	6 (8.5)	0.75
QTd >60 ms (N=46)	18 (30)	28 (39.4)	0.27

QTc: corrected QT interval; QTd: QT dispersion; ms: milliseconds

Table 4 Comparison of IL-1β, IL-6, hsCRP, C3, C4, and SLEDAI-2K in those with and without prolonged QTc, QTd

Variables	QTc ≥440 ms (n=24)	QTc <440 ms, n= 116	p
IL-1β (pg/mL), median (IQR)	0.1 (0.1-5.7)	0.1 (0.1-3.3)	0.91
IL-6 (pg/mL), median (IQR)	9.1 (2.3- 40.4)	6 (1.5-6)	0.26
hsCRP (mg/dL), median (IQR)	3.14 (3.14-5.27)	3.14 (3.14-8.2)	0.14
C3 (g/L), mean ± SD	0.63 ± 0.45	0.67 ± 0.45	0.99
C4 (g/L), median (IQR)	0.13 (0.66-0.4)	0.13 (0.66-0.4)	0.21
SLEDAI-2K, median (IQR)	11.5 (6.5-16)	12 (8-16)	0.83
Variables	**QTd ≥60 ms, n=50**	**QTd <60 ms, n=90**	**p**
IL-1β (pg/mL), median (IQR)	0.1 (0.1-6.1)	0.1 (0.1-3.3)	0.64
IL-6 (pg/mL), median (IQR)	6.0 (1.5-19.1)	6.6 (2-6.6)	0.91
hsCRP (mg/dL), median(IQR)	3.14 (3.14-6.62)	3.14 (3.14-6.78)	0.61
C3 (g/L), mean ± SD	0.64 ± 0.37	0.68 ± 0.49	0.87
C4 (g/L), median (IQR)	0.087 (0.60-0.32)	0.14 (0.06-6.78)	0.12
SLEDAI-2K, median (IQR)	12.5 (8-16)	12 (7-16.5)	0.9

IL-1β: interleukin 1 beta; IL-6: interleukin 6; C3 and C4: serum complements; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; QTc: corrected QT interval; QTd: QT dispersion; hsCRP: highly sensitive C-reactive protein; IQR: interquartile range; SD: standard deviation

Table 5 none of the variables were predictors of prolonged QTc. However, having valvular regurgitation is associated with a significant reduction in odds of having prolonged QTd in SLE patients, adjusted OR 0.33 (CI 0.14-0.83) p=0.018. Similarly, the presence of hypercholesterolemia is associated with a significant reduction in odds of having prolonged QTd, adjusted OR 0.19 (CI 0.05-0.80) p=0.023. Those patients with high LDL cholesterol and those with hypertriglyceridemia had significantly higher odds of a normal QTd with adjusted OR of 4.34 (1.31-14.46) and 5.59 (1.62-19.38) respectively.

Discussion

The main observations from our study are the presence of prolonged QTc in 17.1%, increased QTd in 35.7%, and non-specific ST-T changes in 7.5%. In the SLICC cohort comprising 779 SLE patients, non-specific ST-T changes were seen in 31%, supraventricular arrhythmias in 1.3%, LVH in 5.4%.[12] A study from New York on 50 SLE patients with mean age of 36 years and median disease duration of 6 years found non-specific ST-T changes in 56% lupus compared to 17% rheumatoid arthritis (RA).[18] This study suggests that high prevalence of ST-T changes is a reflection of atherosclerosis

Table 5 Multivariable binary logistic regression analyses for QTc/QTd with clinical and laboratory variables

Variables	QTc ≥440 ms, n=24	QTc <440 ms, n= 116	Adjusted OR (95% CI)	p	QTd ≥60 ms, n=50	QTd <60 ms, n= 90	Adjusted OR (95%CI)	p
Active lupus[a]	21 (87.5)	99 (85.3)	0.39 (0.06-2.48)	0.322	43 (86)	77 (85.6)	0.77 (0.18-3.26)	0.721
High disease activity[b]	14 (58.3)	70 (60.3)	1.16 (0.34-3.91)	0.814	29 (58)	54 (61)	1.42 (0.48-41,19)	0.528
SLE disease duration <2 years	20 (83.3)	99 85.3)	0.62 (0.15-2.58)	0.512	42 (84)	77 (85.6)	0.67 (0.19-2.29)	0.520
Lupus nephritis	9 (37.5)	48 (41.4)	1.75 (0.47-6.56)	0.402	23 (46)	34 (37.8)	0.43 (0.15-1.25)	0.120
Mucocutaneous	12 (50)	84 (72.4)	2.31 (0.68-7.86)	0.181	27 (54)	69 (76)	2.09 (0.77-5.68)	0.148
Low C3 (C3 <0.9 g/L)	17 (70)	80 (68.9)	0.93 (0.29-2.91)	0.907	37 (74)	60 (66)	0.49 (0.19-1.31)	0.157
Low C4 (C4 <0.1 g/L)	11 (46)	62 (53.4)	1.29 (0.37-4.53)	0.683	28 (56)	45 (50)	1.13 (0.41-3.11)	0.820
Anti-Ro/SSA	11 (45.8)	52 (44.8)	0.79 (0.25-2.44)	0.680	20 (40)	43 (48)	1.74 (0.69-4.39)	0.238
Anti-La/SSB	3 (12.5)	31 (26.7)	2.33 (0.51-10.56)	0.273	9 (18)	25 (28)	1.21 (0.41-3.560)	0.727
Valvular regurgitation	11 (45.8)	37 (31.9)	0.56 (0.19-1.59)	0.278	22 (44)	26 (29)	0.33 (0.14-0.83)	0.018
Hypertension	7 (29.1)	32 (23.8)	1.02 (0.27-3.86)	0.975	13 (26)	26 (29)	2.63 (0.84-8.27)	0.098
Total cholesterol >200 mg/dL	7 (29)	24 (20.6)	0.42 (0.07-2.43)	0.330	13 (26)	21 (23)	0.19 (0.05-0.80)	0.023
HDL-C <40 mg/dL in men and <50 mg/dL in women	8 (33)	61 (52.5)	2.72 (0.68-10.87)	0.157	21 (42)	48 (53)	0.89 (0.31-2.56)	0.842
LDL-C >100 mg/dL	6 (25)	38 (32.7)	2.34 (0.45-11.01)	0.321	11 (22)	33 (36)	4.34 (1.31-14.46)	0.017
Triglycerides >250 mg/dL	9 (37.5)	46 (39.6)	0.92 (0.19-4.37)	0.920	14 (28)	41 (45)	5.59 (1.62-19.38)	0.007
hsCRP >3.14 mg/dL	7 (29)	54 (46)	2.44 (0.78-7.58)	0.123	22 (44)	39 (43)	1.29 (0.56-3.03)	0.547

Values are expressed in n (%). OR (CI): odds ratio (confidence interval); ms: milliseconds; LVEF: left ventricular ejection fraction; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; hsCRP: highly sensitive C-reactive protein; C3 and C4: serum complements C3 and C4 respectively. [a]Active lupus was defined as SLEDAI-2K >4; [b]High disease activity was defined as SLEDAI-2K ≥10

and cardiovascular disease burden in lupus patients who have longer disease duration. In contrast we observed non-specific ST-T changes in 7.5% of our patients who were also a decade younger and had a disease duration of only 8 months.

In 2005, Pineau et al reported that prolonged QTc (defined as QTc ≥440 ms) was prevalent in 16% SLE patients.[5] In 2011 the same group in a two-phase study reported a much lower prevalence of prolonged QTc. In the first phase of the study prolonged QTc was present in 7.3%, while in the study's second phase, prolonged QTc was observed in only 6.5%.[19] Though the frequency of prolonged QTc was low, there was a significant association with anti-Ro positivity. Data from the SLICC cohort showed that prolonged QTc and QTd was found in 20.3% and 37% respectively.[12] The median SLE disease duration in the SLICC cohort was 10 months.[12] Our findings appeared similar to those reported by the SLICC group. We observed prolonged QTc and increased QTd in 17.1% and 35.7% respectively, our patients too were young, predominantly with early lupus. Contrastingly, Sham et al reported that 51 of 100 (51%) HCQ naïve, newly diagnosed SLE patients had QTc >440 ms, while QTd prolongation was present in only 6%.[11]

The association of ventricular repolarisation abnormalities with anti-Ro was initially studied among connective tissue diseases (CTDs) patients comprising of SLE, mixed connective tissue disease (MCTD), scleroderma and undifferentiated connective tissue disease (UCTD).[20] In a study comprising 57 patients with CTDs, Lazzarini et al reported that 58% anti-Ro positive CTDs patients had QTc >440ms and none in the anti-Ro negative group.[20] They also demonstrated that the length of the QTc was correlated with anti-Ro titres.[21] In 2007 the same

group reported the findings of a 24-hour ambulatory ECG of 46 patients with CTD, where they confirmed the association of QTc prolongation with anti-Ro positivity.[22] In addition anti-Ro positive CTD patients had higher incidence of ventricular arrhythmia, which authors attributed to QTc prolongation.[22]

We however did not find any association of QTc or QTd with anti-Ro positivity. This absence of association between anti-Ro and QTc/QTd prolongation was also reported by others.[12,18,23] In the study by Gordon et al, the mean QTc was found to be slightly longer in anti-Ro positive CTD patients but it was not significant.[23] Similarly the SLICC group reported that prolonged QTc was not associated with anti-Ro positive status.[12] Likewise the study from New York showed no association of QTc with anti-Ro.[18]

Apart from anti-Ro status, ventricular repolarisation abnormalities have been associated with active lupus.[11,24] An Iranian group reported that QTd was significantly higher in patients with high disease activity.[24] The SLICC cohort study did not mention an association of QTc with disease activity.[12] We too found no such associations of QTc with disease activity nor with other clinical features.

In our study some unexpected findings with regards to QTd were noted. Patients with valvular regurgitation and hypercholesterolemia had significantly reduced odds of having increased QTd. Furthermore, those with high LDL cholesterol and hypertriglyceridemia had significantly higher odds of having a normal QTd. These findings are contrary to what increased QTd is typically associated with.[7,15,16] We are unable to suitably explain the basis of these findings.

Prolongation of QTc has been correlated with inflammatory markers such as CRP and inflammatory cytokines in RA.[25] In our study IL-1β and IL-6 concentrations in our SLE patients varied widely and we found no significant correlations of IL-1β and IL-6 with either QTc or QTd. Pisoni et al in a study of 73 CTD (55 anti-Ro positive and 18 anti-Ro negative) showed higher prevalence of QTc prolongation in anti-Ro group. Moreover, median IL-1β concentrations were significantly higher in those with prolonged QTc ($p=0.006$).[26] This study suggests that excess inflammatory cytokines has led to QTc prolongation. There is also evidence that cytokines via excessive oxidative stress, cause ventricular repolarization abnormalities in the cardiac myocyte.[27] An experimental study demonstrated that IL-6 causes inhibition of the K channel (the target channel that has a predominant role in cardiac repolarisation).[28]

Overall, our results are similar to previous studies that did not demonstrate association of QTc or QTd with anti-Ro antibodies.[12,18,23] However, our study has several limitations. Firstly, since QT interval was calculated manually, assessment of the exact ending of T-wave was difficult and prone to errors. However, many QT experts say that manual calculation of QT interval is less prone to errors when compared to automated QT calculation.[14] Secondly, we did not analyse the cause of sinus tachycardia in these patients. Some patients would have had fever or an infection that would otherwise explain the tachycardia. Thirdly, ideally a 24-hour-ECG monitoring should have been done so that we could have detected diurnal variations of ECG intervals. In this context, a long-term monitoring to detect possible arrhythmia due to prolonged QTc is planned. Lastly, because of the small number of patients with prolonged QTc we did not analyse the relationship of QT prolongation with antihypertensive drugs and diabetes.

At the time of writing this paper, there were many reports of QT interval prolongation in a small proportion of individuals who received chloroquine or HCQ for treatment of coronavirus disease 2019 (COVID-19).[29] This occurred mostly in critically ill patients who had electrolyte imbalance and were concomitantly receiving medication that could potentially prolong QT.[30,31] Because we had not planned to study the effect of HCQ on QTc/QTd prolongation, we are unable to say whether HCQ contributed to QT prolongation. One study had shown that prolonged QTc in patients with active SLE disease returned to normal with treatment, thus giving indirect evidence that HCQ is protective in lupus and QTc prolongation was due to lupus disease.[11] HCQ is also known to significantly reduce the risk of recurrence of cardiac neonatal lupus.[32] Though long term experience of rheumatologists with HCQ is reassuring regarding the safety, this drug is not without risk.[33] Therefore before administering HCQ (or other drugs) off label for any condition (including COVID-19) the risk benefit ratio has to be considered. In the case of lupus the benefits of HCQ clearly outweigh the risk.[34]

To conclude, we observed that 17% and 35% SLE patients have QTc and QTd prolongation respectively, but an association with anti-Ro antibodies or disease activity was not found. A large proportion had other asymptomatic ECG abnormalities that may be a reflection of subclinical cardiac involvement. A careful clinical follow up of these patients who have prolonged QT parameters is required because abnormal QT parameters in the general population are known to predispose sudden cardiac death.

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