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Evidence for cardiac safety and antiarrhythmic potential of chloroquine in systemic lupus erythematosus

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Aims To perform a comprehensive evaluation of heart rhythm disorders and the influence of disease/therapy factors in a large systemic lupus erythematosus (SLE) cohort.

Methods and results Three hundred and seventeen consecutive patients of an ongoing electronic database protocol were evaluated by resting electrocardiogram and 142 were randomly selected for 24 h *Holter* monitoring for arrhythmia and conduction disturbances. The mean age was 40.2 ± 12.1 years and disease duration was11.4 ± 8.1 years. Chloroquine (CQ) therapy was identified in 69.7% with a mean use of 8.5 ± 6.7 years. Electrocardiogram abnormalities were detected in 66 patients (20.8%): prolonged QTc/QTd (14.2%); bundle-branch block (2.5%); and atrioventricular block (AVB) (1.6%). Age was associated with AVB ($P = 0.029$) and prolonged QTc/QTd ($P = 0.039$) whereas anti-Ro/SS-A and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores were not ($P > 0.05$). Chloroquine was negatively associated with AVB ($P = 0.01$) as was its longer use (6.1 ± 6.9 vs. 1.0 ± 2.5 years, $P = 0.018$). Time of CQ use was related with the absence of AVB [odds ratio (OR) = 0.103; 95% confidence interval (CI) = 0.011–0.934, $P = 0.043$] in multiple logistic regression. Holter monitoring revealed abnormalities in 121 patients (85.2%): supraventricular ectopies (63.4%) and tachyarrhythmia (18.3%); ventricular ectopies (45.8%). Atrial tachycardia/fibrillation (AT/AF) were associated with shorter CQ duration (7.05 ± 7.99 vs. 3.63 ± 5.02 years, $P = 0.043$) with a trend to less CQ use ($P = 0.054$), and older age ($P < 0.001$). Predictors of AT/AF in multiple logistic regression were age (OR = 1.115; 95% CI = 1.059–1.174, $P < 0.001$) and anti-Ro/SS-A (OR = 0.172; 95% CI = 0.047–0.629, $P = 0.008$).

Conclusions Chloroquine seems to play a protective role in the unexpected high rate of cardiac arrhythmias and conduction disturbances observed in SLE. Further studies are necessary to determine if this antiarrhythmic effect is due to the disease control or a direct effect of the drug.

Keywords Antimalarial • Arrhythmia • Safety • Treatment • Systemic lupus erythematosus

Introduction

Heart rhythm disorders (HRDs) have been documented in small systemic lupus erythematosus (SLE) series and seem to occur in ~10% of cases, either alone or in association with other heart conditions.[1] Rhythm and conduction disturbances as well as sudden cardiac death in SLE have higher incidence than expected in the general population.[2]

Conduction abnormalities such as atrioventricular block (AVB), intraventricular (IV) disturbances, and prolonged QT interval have already been described in case reports and a few studies without concomitant Holter evaluation of arrhythmias.[3–5] Recently, increased QTd was described in SLE[5,6] and seems to be associated with disease activity [Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores] in SLE, but was not identified in patients under hydroxychloroquine.[6]

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What's new?

- Systemic lupus erythematosus (SLE) patients have a high rate of rhythm and conduction disturbances.
- The antiarrhythmic effect of chloroquine may be due to disease control or a direct effect of the drug.
- The present paper suggested that chloroquine plays a protective role in arrhythmias observed in SLE.

Heart rhythm disorder can be related with coronary artery disease, myocarditis, or small vessel vasculitis with collagen deposition and fibrosis affecting the conduction system in SLE.[2,7–9] A possible role of autoantibodies such as anti-SS-A/Ro on the pathogenesis of HRD in adult SLE patients has also been suggested.[10–12] With regard to antimalarial cardiotoxicity,[13,14] rare cases of third-degree AVB with consequent syncope episodes have been reported.[15] In contrast, in patients with connective tissue diseases (CTDs) using hydroxychloroquine this toxicity was not confirmed by electrocardiogram (ECG) evaluation.[16] Similarly, a recent prospective study of 28 SLE patients with 7-month chloroquine (CQ) treatment also demonstrated no significant changes using ECG and Holter monitoring.[17] Moreover, the reduction of ventricular ectopy with CQ which recurred after discontinuation in five patients provides evidence for antiarrhythmic action of this drug.[18]

The aim of the present study was therefore to perform a comprehensive evaluation of HRDs in a large SLE population and to determine the potential role of disease factors and therapy, particularly CQ.

Patients and methods

A descriptive, observational, open clinical study was performed with patients regularly followed at the outpatient Lupus Clinic, Rheumatology Division of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. Since 1999, a standard electronic protocol has been conducted at 1- to 6-month intervals and consisted of an extensive clinical, laboratorial, and treatment evaluation of 1145 SLE patients, including relevant data for this study. The protocol was approved by the local Institutional Review Board, and all the participants signed the informed consent.

All 369 adult patients (age >18 years old) selected for this study fulfiled the American College of Rheumatology 1997 revised criteria for SLE.[19] Exclusion criteria were primary cardiopathy, coronary and Chagas disease, and previous history of heart surgery and pacemaker. At entry, SLE patients with uncontrolled systemic hypertension, current myocarditis, or heart failure were also excluded.

A total of 317 SLE patients were evaluated for this study since fifty-two had to be excluded due to the use of medications potentially involved in HRD [fluoxetine ($n = 26$), diltiazem ($n = 13$), amitriptyline ($n = 12$), chlortalidone ($n = 10$), hydrochlorothiazide ($n = 9$), atenolol ($n = 6$), sertraline ($n = 6$), chlorpromazine ($n = 3$), fluconazole ($n = 2$), furosemide ($n = 2$), propranolol ($n = 2$), metoprolol ($n = 1$), terbutaline ($n = 1$), and verapamil ($n = 1$)].

At entry, a clinical and laboratory evaluation was performed in these 317 SLE patients, including disease activity according to the SLEDAI,[20] which was arbitrarily defined as SLEDAI scores ≥8. Current therapy was recorded and also included chloroquine diphosphate (CQ) use.

Electrocardiogram analysis

Resting standard 12-lead ECG (GE/Marquette®, MAC 1200®, GE Healthcare) was performed in all SLE patients with automatic measurements confirmed by manual technique by the same professional. Measurement of the ECG parameters was performed by a trained cardiologist (R.A.T.) blinded to the clinical characteristics of the patients. Heart rhythm and conduction disturbances were analysed and recorded for each patient. The main ECG alterations were defined as: bradycardia (HR < 50 b.p.m.); tachycardia (HR > 100 b.p.m.); AVB (first, second, or third degree); wide QRS (>120 ms); QTc > 500 ms or QT dispersion (QTd) > 65 ms (when QTc was between 440 and 500 ms).[21]

Holter monitoring analysis

Half of the enroled patients were randomly selected to 24 h *Holter* monitoring (12-channel, digital—DMS® Cardioscan-12, recorder 300-7). The evaluation was also performed by the same blinded trained cardiologist (R.A.T.). Heart rhythm and conduction disturbances were analysed and recorded for each patient. The main *Holter* alterations were defined as: supraventricular ectopy (low rate: <30/h, or high rate: >30/h); supraventricular tachyarrhythmia [atrial tachycardia (AT), atrial fibrillation (AF)—any episode with at least 10 s duration]; ventricular ectopy (low rate: <30/h, or high rate: >30/h); and ventricular tachycardia (VT); pauses (>2 s).

Laboratory evaluation

At entry, serum samples of all SLE patients were obtained after a 12 h overnight fasting to perform inflammatory and immunological tests. C-reactive protein (CRP) levels were determined by nephelometry and erythrocyte sedimentation rate (ESR) was evaluated using Westergren method.

Serum immunological analysis

Antinuclear antibodies were detected by indirect immunofluorescence (IIF) using HEp-2 cells as substrate. Anti-double-stranded DNA (dsDNA) was also detected by IIF using *Crithidia luciliae*. Detection of autoantibodies to saline-soluble antigens, Ro/SS-A, and La/SS-B, was performed by counterimmunoelectrophoresis against dog spleen extract.[22] Monospecific reference sera were included in each assay to characterize autoantibody specificity. Serum levels of C3 and C4 complement fractions were measured by radial immunodiffusion (SIEMENS Health Care).

Statistical analysis

Results are presented as the mean ± standard deviation (SD) or percentage. Data were analysed by Student's *t*-test or Mann–Whitney's *U* test to evaluate differences between the two groups. Comparisons between proportions were calculated using χ^2 test or Fisher's exact test. The receiver-operator characteristic curve was used to identify the cut-off value for the quantitative variables predictor of HRD. Variables with a descriptive level of probability considered significant were used to compose the multiple logistic regressions. Statistical significance was set as $P < 0.05$.

Results

Three-hundred and seventeen SLE patients completed the study and the main demographic characteristics are summarized in *Table 1*, with a clear predominance of female gender (91.5%). The mean age was 40.2 ± 12.1 years and the mean disease duration

Table 1 Demographic and laboratorial characteristics of SLE patients

Parameter	*N* = 317
Age (years)	40.2 ± 12.1
Female, *n* (%)	290 (91.5%)
Disease duration (years)	11.4 ± 8.1
SLEDAI score	1.04 ± 2.14
SLEDAI ≥ 8, *n* (%)	6 (1.9%)
C3 < 80 mg%, *n* (%)	53 (16.7%)
C4 < 20 mg%, *n* (%)	182 (57.4%)
Anti-dsDNA, *n* (%)	108 (34.1%)
Anti-Ro/SS-A, *n* (%)	111 (35.0%)
Chloroquine use, *n* (%)	221 (69.7%)
Time of chloroquine use (years)	8.5 ± 6.7

Values expressed in mean ± SD or percentage.

was 11.4 ± 8.1 years. Controlled systemic hypertension was identified in 60 patients (18.9%). At entry, the mean SLEDAI score was 1.04 ± 2.14 and only six SLE patients (1.9%) had SLEDAI scores ≥8 (*Table 1*). More than one-third of the patients (34.1%) had positive anti-dsDNA, whereas 57.4% had low C4 and 16.7% had low C3 levels (*Table 1*). Elevated inflammatory markers such as CRP (>3.0 mg/L) and ESR (>12 mm/h) were detected in 40.7 and 51.4%, respectively.

Further analysis of conditions that may contribute to HRD revealed that more than one-third of the patients had anti-Ro/SS-A (35%) (*Table 1*) and 4.1% had anti-La/SS-B antibodies. At entry, current CQ use was identified in 221 SLE patients (69.7%) with a mean time of 8.5 ± 6.7 years (*Table 1*).

The overall analysis of lupus disease therapies revealed that 95 patients were under glucocorticoids (30%), with a current mean prednisone dose of 5.5 ± 2.6 mg/day. Eighty-five patients were using immunosuppressors (27%) with the following distribution among them: 52 azathioprine (16.4%), 11 mycophenolate mofetil (3.5%), 19 methotrexate (6.0%), and 2 cyclophosphamide (0.6%).

Electrocardiogram and Holter evaluation

Among the 317 SLE patients, resting-ECG abnormalities were detected in 66 patients (20.8%). Heart rhythm alterations on ECG were observed in 2.9%: 1.3% sinus bradycardia and 1.6% tachycardia (*Table 2*). The mean heart rate was 70.5 ± 11.4 b.p.m. The main conduction disturbances observed were prolonged QTc/QTd in 14.2% followed by IV conduction disturbances in 2.5% (*Table 2*). The mean PR interval was 147.8 ± 21.4 ms (96–236 ms), the mean QTc was 443.2 ± 25.3 ms (373–518 ms), and the mean QTd was 51.4 ± 20.1 ms (12–108 ms). Ten patients had prolonged QTc (3.1%) and 35 had increased QTd (11.0%). Atrioventricular block was identified in five SLE patients (1.6%) (*Table 2*) and only one of these patients was using CQ.

Abnormalities were detected in 121 patients (85.2%) among the 142 SLE patients that performed *Holter* monitoring. Forty-five patients had bradycardia (31.7%) and eight tachycardia (5.6%).

Table 2 Heart rhythm disorders according to resting ECG and 24 h *Holter* monitoring in SLE patients

ECG	*N* = 317
Any abnormality	66 (20.8%)
Rhythm	
Bradycardia	4 (1.3%)
Tachycardia	5 (1.6%)
Sinusal	4 (1.3%)
Supraventricular	1 (0.3%)
Conduction	
Atrioventricular block (first degree)	5 (1.6%)
Intraventricular conduction disturbances	8 (2.5%)
Right bundle-branch block	6 (1.9%)
Left bundle-branch block	2 (0.6%)
Prolonged QTc/QTd	45 (14.2%)
Holter	*N* = 142
Any abnormality	121 (85.2%)
Rhythm	
Bradycardia	45 (31.7%)
Tachycardia	8 (5.6%)
Arrhythmia	
Supraventricular ectopies	90 (63.4%)
High rate (>30/h)	2 (1.4%)
Supraventricular tachyarrhythmias	26 (18.3%)
Atrial tachycardia	22 (15.5%)
Atrial fibrillation	4 (2.8%)
Ventricular ectopies	65 (45.8%)
High rate (>30/h)	6 (4.2%)
Ventricular tachycardia	4 (2.8%)
Pauses	4 (2.8%)

Values expressed in percentage.

Supraventricular ectopies were the most common abnormality identified in 90 patients (63.4%), whereas ventricular ectopies were observed in 65 SLE patients (45.8%). Six patients (4.2%) had a high rate of ventricular ectopies (>30/h) and four (2.8%) had episodes of non-sustained VT (only one of them had a high rate of ventricular ectopies associated with VT), with a 6.3% rate of complex ventricular arrhythmia. Twenty-six patients (20.4%) had episodes of supraventricular tachyarrhythmia: AT in 15.5% and AF in 2.8%. Pauses were detected in only four patients (2.8%) (*Table 2*). Rhythm and conduction abnormalities were not related with the use of steroids and immunosuppressive drugs.

Influence of disease factors and therapy on electrocardiogram

The influence of age, CQ therapy, anti-Ro/SS-A, and disease activity (SLEDAI ≥ 8) in rhythm and conduction ECG parameters is illustrated in *Table 3*. Age was significantly associated with AVB (42.3 ± 13.2 vs. 54.2 ± 7.3 years, $P = 0.029$), prolonged QRS (41.8 ± 13.2 vs. 60.2 ± 10.5 years, $P < 0.001$), and prolonged

Table 3 Influence of risk factors on main abnormalities of resting ECG and 24 h Holter monitoring in SLE patients

ECG abnormality	Prolonged QRS			Prolonged QTc			AVB		
	+	−	P	+	−	P	+	−	P
	n = 8	n = 309		n = 10	n = 307		n = 5	n = 312	
Age (years)	60.2 ± 10.5	41.8 ± 13.2	<0.001	51.0 ± 10.7	42.1 ± 13.4	0.039	54.2 ± 7.3	42.3 ± 13.2	0.029
Chloroquine use, n (%)	5 (62.5%)	217 (70.2%)	0.46	8 (80%)	214 (69.7%)	0.73	1 (20%)	221 (70.8%)	0.01
Time of chloroquine use (years)	4.6 ± 5.9	6.0 ± 6.9	0.49	11.4 ± 10.4	5.8 ± 6.7	0.08	1.0 ± 2.4	6.1 ± 6.8	0.018
Anti-Ro/SS-A, n (%)	5 (62.5%)	108 (34.9%)	0.29	4 (40%)	109 (35.5%)	0.75	2 (40%)	110 (35.3%)	1.00
Disease activity (SLEDAI ≥ 8), n (%)	1 (12.5%)	84 (27.2%)	0.45	2 (25%)	83 (27%)	1.00	2 (40%)	82 (26.3%)	0.66
Holter abnormality	AT/AF			VE (>30/h)			VT		
	+	−	P	+	−	P	+	−	P
	n = 26	n = 116		n = 6	n = 136		n = 4	n = 138	
Age (years)	52.5 ± 12.0	40.2 ± 11.5	<0.001	48.4 ± 10.2	41.9 ± 12.5	0.25	49.5 ± 24.3	41.9 ± 12.0	0.23
Chloroquine use, n (%)	11 (42.3%)	83 (71.6%)	0.054	1 (16.7%)	93 (68.4%)	0.038	1 (25%)	93 (67.4%)	0.1
Time of chloroquine use (years)	3.6 ± 5.0	7.0 ± 8.0	0.043	3.0 ± 6.7	6.6 ± 7.7	0.09	2.2 ± 4.5	6.6 ± 7.7	0.13
Anti-Ro/SS-A, n (%)	4 (15.4%)	48 (41.4%)	0.042	1 (16.7%)	51 (37.5%)	0.65	1 (25%)	51 (37%)	0.52
Disease activity (SLEDAI ≥ 8), n (%)	0 (0%)	1 (0.8%)	0.51	0 (0%)	1 (0.7%)	0.61	0 (0%)	1 (0.7%)	0.71

Values expressed in mean ± SD or percentage.
AVB, atrioventricular block; AT, atrial tachycardia; AF, atrial fibrillation; VE, ventricular ectopies; VT, ventricular tachycardia; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

QTc/QTd (51.0 ± 10.7 vs. 42.1 ± 13.4 years, $P = 0.039$) (*Table 3*). The presence of anti-Ro/SS-A and disease activity (SLEDAI ≥ 8) was not related with any ECG abnormality ($P > 0.05$) (*Table 3*).

Chloroquine use was significantly associated with the absence of AVB (70.8 vs. 20%, $P = 0.01$) but not with prolonged QTc/QTd (80 vs. 69.7%, $P = 0.73$). Reinforcing this finding, the longer use of this drug was negatively associated with AVB (6.1 ± 6.9 vs. 1.0 ± 2.5 years, $P = 0.018$) (*Table 3*). Moreover, multiple logistic regression determined that time of CQ use was related with the absence of AVB [odds ratio (OR) = 0.103; 95% confidence interval (CI) = 0.011–0.934, $P = 0.043$].

Influence of disease factors and therapy on Holter

The influence of age, CQ therapy, anti-Ro/SS-A, and disease activity (SLEDAI ≥ 8) in rhythm and conduction Holter parameters is illustrated in *Table 3*. Age was significantly associated with AT/AF (52.5 ± 12.0 vs. 40.2 ± 11.5 years, $P < 0.001$), whereas the presence of anti-Ro/SS-A was negatively related with this parameter (41.4 vs. 15.4%, $P = 0.042$). Disease activity was not associated with rhythm or conduction abnormalities on Holter ($P > 0.05$) (*Table 3*).

A higher frequency of CQ use was observed in patients without AT/AF with a trend in significance (71.6 vs. 42.3%, $P = 0.054$) reinforced by the finding that longer time of CQ use was associated with the absence of this arrhythmia (7.0 ± 8.0 vs. 3.6 ± 5.0 years, $P = 0.043$) (*Table 3*). Ventricular ectopies were also less frequently observed in patients taking CQ (16.7 vs. 68.4%, $P = 0.038$) (*Table 3*).

The predictors of AT/AF in multiple logistic regression were age (OR = 1.115; 95% CI = 1.059–1.174, $P < 0.001$), while anti-Ro/SS-A were protective (OR = 0.172; 95% CI = 0.047–0.629, $P = 0.008$).

Discussion

This is the largest study that identifies a high rate of rhythm and conduction disturbances in SLE and suggests that CQ may have beneficial electrophysiological properties, particularly in high-risk arrhythmia.

In the present study, 20.8% of the SLE patients demonstrated HRD in resting ECG. This is in accordance with the findings of Godeau *et al.*[23] that detected conduction disorders in 17.5% of 112 patients (103 with SLE), but we have not observed the reported association with disease activity probably due to the low percentage of patients with high SLEDAI in our sample. Moreover, SLEDAI score ≥8 indicates a more severe disease activity. A frequency of 35.7% in ECG abnormalities was, however, found in a study with 140 SLE patients.[4] This higher frequency is probably related with the presence of comorbidities since more than a half of their patients (51.4%) had arterial hypertension, whereas only approximately one-fifth of our patients had controlled hypertension. Reinforcing this possibility, Rhodus *et al.*[24] found ECG abnormalities in 61.5% in whom 76.9% reported previous cardiopathy.

The identification of rhythm and conduction disturbances in SLE seems important since these conditions are related with sudden cardiac death in these patients.[4] Indeed, in a Chinese cohort with 566 patients evaluated for >30 years, ECG alterations were identified as independent risk factors for death.[25]

Prolonged QRS and QT interval were the most common abnormalities in ECG observed herein and confirm the high frequency observed in previous reports in SLE.[4] Regarding possible risk factors, only age was associated with these ECG alterations in our study and was related with the prolonged QT interval in a previous study.[4] Increased QTc/QTd is strongly associated with ventricular arrhythmias and sudden cardiac death in several cardiac and other comorbidities[26,27] and deserves special attention in SLE.

In our large cohort study, 24 h Holter monitoring allowed the recognition of HRD in almost 85% of the SLE patients, which is much higher than previously described.[1] Supraventricular and ventricular ectopies were the most common abnormalities and were observed in approximately two-thirds and half of the studied SLE patients, respectively. Since most of our patients had inactive lupus, disease activity (SLEDAI scores) did not account for ECG and Holter abnormalities identified in this study and could be even higher than observed herein.

The most important finding of our Holter study was the high frequency of non-sustained and sustained episodes of supraventricular tachyarrhythmia, such as AT and AF. Indeed, AF was recently described to be associated with SLE and a 1.72-increased risk was detected in patients older than 65 years old compared with healthy controls after adjusting for age and comorbidities in a study of 4 16 786 discharges using the Nationwide Inpatient Sample Database.[28] More importantly, it is well-known that AF is the most frequent sustained cardiac arrhythmia affecting 1–2% of the general population and is associated with ischaemic central nervous system events and sudden death.[29] As expected, in our study, the presence of AT/AF was also closely related with age.

Surprisingly, supraventricular tachyarrhythmias were associated with the lower frequency of anti-Ro/SS-A. The role of these antibodies in the pathogenesis of HRD in SLE patients has been suggested but it is still controversial in the literature. In a previous evaluation of 46 patients with CTDs, anti-Ro/SS-A-positive patients demonstrated QTc interval prolongation that was persistent throughout a 24 h observation period.[10] In SLE, a recent cross-sectional analysis with 150 patients showed an association of prolonged QTc with anti-Ro/SS-A (adjusted OR 12.6; 95% CI 2.3, 70.7).[30] In the present study, long QTc was defined according to increased risk for arrhythmias, which is markedly associated with QTc $>$500 ms,[29] longer than the limit used by these authors. Moreover, these antibodies were detected by ELISA that is a more sensitive method than counterimmunoelectrophoresis. Using this latter method, the presence of anti-Ro/SS-A in our SLE cohort was not associated with prolonged QRS/QT or other rhythm/conduction abnormalities and, in fact, was associated with less tachyarrhythmia (AT/AF).

Our study provides relevant data about antimalarial cardiac long-term safety use and extends previous observations,[16,17] despite isolated case reports of its cardiotoxicity.[13,14,31,32] In fact, AVB was more commonly observed herein in SLE patients not using antimalarials and also in those with a shorter time of CQ therapy. In addition, this drug was not associated with prolonged QRS or QT on resting ECG in our study. Indeed, cardiac safety of antimalarials was previously suggested in a prospective study with 28 SLE patients that demonstrated no significant changes in ECG and Holter after 7 months of CQ use.[17] In addition, it also extends the observation of no changes of PR and QTc intervals in ECG after a minimum of 1 year of antimalarial therapy in 85 patients with CTDs.[16] Finally, the increased QTd described in SLE were not identified in patients that received hydroxychloroquine.[6]

Besides safety, our findings also introduce CQ as having a potential antiarrhythmic in SLE. In fact, the most striking finding identified herein was the association of the low frequency of AT/AF with longer time of CQ use and a trend of significance with the presence of this therapy. Moreover, a high rate of ventricular ectopies was also observed in those that were not using this therapy. These findings support the notion that CQ prevents the appearance of these high-risk arrhythmias and this effect could possibly be time dependent. In fact, a prospective study to determine the effectiveness of antimalarials in the treatment of supraventricular paroxysmal tachycardia, multifocal ventricular extrasystoles and AF was conducted in the late 50s.[33] In this study, 73 arrhythmias were treated with CQ and hydroxychloroquine and more than two-thirds ($n = 50$) responded favourably with restoration of sinus rhythm. Interestingly, reversal of AF was observed in 23 of the 42 cases with this arrhythmia, which raised the possibility of antimalarial use as an effective treatment.[33] Further clinical evidence of antiarrhythmic action after 9 weeks of CQ administration was also observed in subjects with ventricular ectopies which recurred after discontinuation.[18] Interestingly, even foetal exposure to hydroxychloroquine during pregnancy of SLE mothers with anti-Ro/SS-A antibodies seems to decrease the risk of development of cardiac neonatal lupus.[34]

Although the underlying mechanism of this antiarrhythmic action remains unproven, antimalarial could have this effect by the inhibition of phospholipase activity that is also identified with amiodarone.[18] On the other hand, CQ is structurally similar to quinidine and both drugs have been shown to block ion channels. Interestingly, quinidine only partially blocks I(K1) whereas CQ binds at the centre of the ion permeation vestibule of Kir2.1, which makes it a more effective I(K1) blocker and antifibrillatory agent than quinidine.[35] Moreover, inhibition of endosomal acidification required for optimal toll-like receptors signalling could also promote a decrease in cardiac inflammation and scarring.[34]

The present study was designed to identify the frequency of rhythm and conduction disturbances in SLE. The large number of lupus patients evaluated herein by resting ECG and also by Holter monitoring was a great advantage to this purpose, but this evaluation was not performed in the healthy control group. In addition, this study lacks other cardiac tests to rule out the presence of structural heart disease such as cardiac magnetic resonance imaging or Doppler echocardiography. Finally, protective effect observed herein is limited to CQ use and further studies are necessary to also prove this effect with hydroxychloroquine that is an antimalarial drug with the same mechanism of action.

In the light of our findings, CQ seems to play a protective role in the unexpected high rate of cardiac arrhythmias and conduction disturbances observed in SLE. Further studies are necessary to determine if this antiarrhythmogenic effect is due to the disease control or a direct effect of the drug and research to assess if the antimalarial effect on the cardiac cellular electrophysiology is still necessary to prove the potential of this therapy in reducing HRD.

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