

Electrocardiographic Findings in Systemic Lupus Erythematosus: Data From an International Inception Cohort

JOSIANE BOURRÉ-TESSIER,¹ MURRAY B. UROWITZ,² ANN E. CLARKE,³ SASHA BERNATSKY,³ MORI J. KRANTZ,⁴ THAO HUYNH,⁵ LAWRENCE JOSEPH,⁵ PATRICK BELISLE,⁵ SANG-CHEOL BAE,⁶ JOHN G. HANLY,⁷ DANIEL J. WALLACE,⁸ CAROLINE GORDON,⁹ DAVID ISENBERG,¹⁰ ANISUR RAHMAN,¹⁰ DAFNA D. GLADMAN,² PAUL R. FORTIN,¹¹ JOAN T. MERRILL,¹² JUANITA ROMERO-DIAZ,¹³ JORGE SANCHEZ-GUERRERO,¹³ BARRI FESSLER,¹⁴ GRACIELA S. ALARCÓN,¹⁴ KRISTJÁN STEINSSON,¹⁵ IAN N. BRUCE,¹⁶ ELLEN GINZLER,¹⁷ MARY ANNE DOOLEY,¹⁸ OLA NIVED,¹⁹ GUNNAR STURFELT,¹⁹ KENNETH KALUNIAN,²⁰ MANUEL RAMOS-CASALS,²¹ MICHELLE PETRI,²² ASAD ZOMA,²³ AND CHRISTIAN A. PINEAU³

Objective. To estimate the early prevalence of various electrocardiographic (EKG) abnormalities in patients with systemic lupus erythematosus (SLE) and to evaluate possible associations between repolarization changes (increased corrected QT [QTc] and QT dispersion [QTd]) and clinical and laboratory variables, including the anti-Ro/SSA level and specificity (52 or 60 kd).

Methods. We studied adult SLE patients from 19 centers participating in the Systemic Lupus International Collaborating Clinics (SLICC) Inception Registry. Demographics, disease activity (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K]), disease damage (SLICC/American College of Rheumatology Damage Index [SDI]), and laboratory data from the baseline or first followup visit were assessed. Multivariate logistic and linear regression models were used to assess for any cross-sectional associations between anti-Ro/SSA and EKG repolarization abnormalities.

Results. For the 779 patients included, mean \pm SD age was 35.2 ± 13.8 years, 88.4% were women, and mean \pm SD disease duration was 10.5 ± 14.5 months. Mean \pm SD SLEDAI-2K score was 5.4 ± 5.6 and mean \pm SD SDI score was 0.5 ± 1.0 . EKG abnormalities were frequent and included nonspecific ST-T changes (30.9%), possible left ventricular hypertrophy (5.4%), and supraventricular arrhythmias (1.3%). A QTc ≥ 440 msec was found in 15.3%, while a QTc ≥ 460 msec was found in 5.3%. Mean \pm SD QTd was 34.2 ± 14.7 msec and QTd ≥ 40 msec was frequent (38.1%). Neither the specificity nor the level of anti-Ro/SSA was associated with QTc duration or QTd, although confidence intervals were wide. Total SDI was significantly associated with a QTc interval exceeding 440 msec (odds ratio 1.38 [95% confidence interval 1.06, 1.79]).

Conclusion. A substantial proportion of patients with recent-onset SLE exhibited repolarization abnormalities, although severe abnormalities were rare.

INTRODUCTION

Electrocardiography (EKG) is an inexpensive, universally available noninvasive tool that has the potential to detect important systemic lupus erythematosus (SLE)-associated

cardiovascular involvement, including rhythm disturbances and underlying repolarization abnormalities. Abnormal cardiac repolarization is generally assessed by the

The McGill University Health Centre Lupus Cohort was supported in part by the Singer Family Fund for Lupus Research. The Birmingham Lupus Cohort was supported by Lupus UK and the NIHR/Wellcome Trust Clinical Research Facility. Dr. Bae's work was supported by a grant of the Korea Healthcare technology R&D project, Ministry for Health & Welfare, Republic of Korea (A120404). Dr. Hanly's work was supported by a grant from the Canadian Institutes of Health Research (MOP-86526). Dr. Bruce's work was supported by the NIHR Manchester Musculoskeletal Biomedical Research Unit, The NIHR/Wellcome Trust Clinical Research Facility, Manchester Academic Health Science Centre, and Arthritis Research UK.

¹Josiane Bourré-Tessier, MD, MSc, FRCPC: University of Montreal Health Center, Montreal, Quebec, Canada; ²Murray B. Urowitz, MD, FRCPC, Dafna D. Gladman, MD: Toronto Western Hospital, University Health Network, and University of Toronto, Toronto, Ontario, Canada; ³Ann E. Clarke, MD, MSc, FRCPC, Sasha Bernatsky, MD, PhD, FRCPC, Christian A. Pineau, MD, FRCPC: Montreal General Hospital, Montreal, Quebec, Canada; ⁴Mori J. Krantz, MD, FACC: University of Colorado, Denver; ⁵Thao Huynh, MD, PhD, FRCPC, Lawrence Joseph, PhD, Patrick Belisle, MSc: McGill University Health Center, Montreal, Quebec, Canada; ⁶Sang-Cheol Bae, MD, PhD, MPH: Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea; ⁷John G. Hanly, MD: Queen Elizabeth II Health Sciences

Significance & Innovations

- Electrocardiography (EKG) has the potential to detect important systemic lupus erythematosus (SLE)-associated cardiovascular involvement. Although patients were young (mean age 35.2 years) and had a short disease duration (mean 10.5 months), patients in the Systemic Lupus International Collaborating Clinics inception cohort already demonstrated evidence of cardiac abnormalities by EKG, including repolarization abnormalities that confer an increased risk for ventricular arrhythmias and sudden death.
- Although the pathogenic role of anti-Ro/SSA in the fetal heart is well recognized, its effect on the adult heart is uncertain, and previous studies that attempted to examine the relationship between anti-Ro/SSA antibodies and repolarization abnormalities in SLE patients were single center and limited by a relatively small number of participants. We did not demonstrate an association between repolarization abnormalities and the anti-Ro/SSA specificities or level in our large population of 779 SLE patients.

detection of prolongation of the heart rate corrected QT (QTc) interval and increased QT dispersion (QTd), defined as the difference between maximal and minimal QT intervals from different EKG leads. Because these EKG abnormalities may confer an increased risk of ventricular arrhythmias and sudden cardiac death (1,2), early identification may have prognostic value.

Centre and Dalhousie University, Halifax, Nova Scotia, Canada; ⁸Daniel J. Wallace, MD: Cedars-Sinai Medical Center, Los Angeles, California; ⁹Caroline Gordon, MD, FRCP: University of Birmingham, Birmingham, UK; ¹⁰David Isenberg, MD, Anisur Rahman, PhD, FRCP: University College London, London, UK; ¹¹Paul R. Fortin, MD, MPH, FRCPC: Centre Hospitalier Universitaire de Québec, Université Laval, Québec, Québec, Canada; ¹²Joan T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; ¹³Juanita Romero-Diaz, MD, MS, Jorge Sanchez-Guerrero, MD, MS: National Institute of Nutrition, Mexico City, Mexico; ¹⁴Barri Fessler, MD, MSPH, Graciela S. Alarcón, MD, MPH: University of Alabama at Birmingham; ¹⁵Kristján Steinsson, MD, PhD: Landspítali University Hospital, Reykjavik, Iceland; ¹⁶Ian N. Bruce, MD, FRCP: NIHR Manchester Musculoskeletal Biomedical Research Unit, University of Manchester, Manchester, UK; ¹⁷Ellen Ginzler, MD, MPH: State University of New York Health Science Centre, Brooklyn; ¹⁸Mary Anne Dooley, MSc: University of North Carolina, Chapel Hill; ¹⁹Ola Nived, MD, PhD, Gunnar Sturfelt, MD, PhD: University Hospital Lund, Lund, Sweden; ²⁰Kenneth Kalunian, MD: University of California, San Diego; ²¹Manuel Ramos-Casals, MD, PhD: Servicio de Enfermedades Autoinmunes, Barcelona, Spain; ²²Michelle Petri, MD, MPH: Johns Hopkins University, Baltimore, Maryland; ²³Asad Zoma, FRCP: Stonehouse Hospital, Glasgow, UK.

Some evidence suggests that anti-Ro/SSA antibodies, strongly associated with congenital heart block in neonatal lupus, may also lead to QTc prolongation among adults with systemic autoimmune rheumatic diseases (3,4). In addition, the specific anti-Ro/SSA subtype (against 52-kd or 60-kd subunit) as well as its level may be important factors in determining the effect of this autoantibody on the cardiomyocytes, both in the fetus and in adults (5,6). Previous studies that attempted to examine the relationship between anti-Ro/SSA antibodies and QTc prolongation in systemic autoimmune rheumatic diseases were single center and limited by a relatively small number of participants. Therefore, the literature is scant and conflicting, and the effect of anti-Ro/SSA in adults with SLE remains unclear (7,8).

Given this background, we evaluated the prevalence of various EKG abnormalities in a large international inception cohort of patients with SLE and assessed for possible associations between repolarization abnormalities (QTc prolongation and increased QTd) and various clinical and laboratory variables, including the anti-Ro/SSA level and specificity (52 and 60 kd).

MATERIALS AND METHODS

Study population. The Systemic Lupus International Collaborating Clinics (SLICC) is a group of SLE experts who have developed an international registry of newly diagnosed SLE patients, the SLICC Prospective Inception Cohort. The present analysis includes adult patients from 19 centers in 8 different countries participating in this inception cohort. Patients were enrolled within 15 months of their date of diagnosis based on American College of Rheumatology (ACR) classification criteria (9). Patients in this registry are followed prospectively and undergo a yearly research visit, where demographics, disease activity (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K] [10]), disease damage (SLICC/ACR Damage Index [SDI] [11]), clinical features of SLE, coronary artery disease (CAD) risk factors, and laboratory data are collected. Data from centers performing routine annual

Dr. Krantz has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Reckitt/Cardiocre and Abbott Vascular, and (more than \$10,000) from Novo Nordisk. Dr. Bruce has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from GSK, MedImmune, Pfizer, Roche, and UCB. Dr. Nived has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from GSK and UCB. Dr. Sturfelt has received speaking fees (less than \$10,000) from GSK.

Address correspondence to Christian A. Pineau, MD, FRCPC, The Montreal General Hospital, 1650 Cedar Avenue, A6.163, Montreal, Quebec H3G 1A4, Canada. E-mail: Christian.pineau@mcgill.ca.

Submitted for publication January 20, 2014; accepted in revised form May 6, 2014.

12-lead resting EKGs have been used (19 from the 27 centers participating in this cohort in 2008). Participants included in the present analysis had baseline research visits between October 1999 and December 2008.

Study variables. Clinical and laboratory variables from the baseline or the first followup visit were studied as potential factors associated with EKG abnormalities, and included age, sex, disease duration, SLEDAI-2K, SDI, arterial hypertension (>140/90 mm Hg recorded at visit), body mass index, current smoking status, alcohol consumption, history of CAD (including myocardial infarction, percutaneous coronary intervention, and coronary bypass surgery), valvular heart disease, and cardiomyopathy. Relevant medication use that could impact cardiovascular status included nonsteroidal antiinflammatory drugs, antimalarials, antihypertensive agents (diuretics, adrenergic inhibitors, beta-blockers, central alpha agonists, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers), nitrates, lipid-lowering agents, steroids, warfarin, heparin, acetylsalicylic acid, contraceptive pills, hormone replacement, thyroid replacement, and immunosuppressive drugs, including azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide. The following laboratory tests were performed in a central laboratory: calcium, albumin, potassium, and magnesium levels; anti-double-stranded DNA; and anti-extractable nuclear antigen (anti-ENA) profile (anti-Ro/SSA subspecificities [52 kd and 60 kd], anti-La/SSB, anti-Sm, and anti-RNP). The measurement of autoantibodies was performed by addressable laser bead immunoassay (BioPlex 2200; Bio-Rad), which permits the simultaneous detection of all autoantibodies of interest. Patients were classified as positive or negative (cutoff value of ≥ 1.0 autoantibody index as positivity) and the titer of the positivity was measured. Lipid profile (with hyperlipidemia defined as greater than the upper limit of the testing laboratory), glucose (with diabetes mellitus defined as fasting blood glucose >7 mmol/liter), and high-sensitivity C-reactive protein level were measured at local laboratories.

EKG. Depending on the quality of the printout, the 12-lead EKG from either the baseline or the first followup visit (25 mm/second paper speed and 10 mm/mV amplitude) was initially manually interpreted by 3 board-certified cardiologists blinded to any clinical information at an independent central core laboratory. Rhythm, conduction diseases, ST-T changes, chamber hypertrophy, QT interval duration, and QTd were assessed. The QT intervals were assessed without magnification and recorded in milliseconds approximated to the nearest 10 msec. The QT interval was defined as the time between the first deflection from the isoelectric PR interval and the visual return of the T wave to the T-P segment. Measurements immediately following atrial or ventricular premature contractions were avoided. Computer-assisted reading was also performed and interpretations were performed according to International Conference on Harmonisation (ICH) guidelines (12). For those lacking computer-generated QTc, the

median raw QT was used to derive the Bazett QTc interval (13). QTd was defined as the difference between maximal and minimal QT intervals and required a minimum of 8 interpretable leads, as previously described (14). Proportions of patients with QTc prolongation crossing categorical regulatory thresholds according to the ICH guidance document (440 msec, 450 msec, 460 msec, 480 msec, and 500 msec) (12) and increased QTd (defined as >40 msec) were also assessed.

Statistical analyses. Descriptive statistics are shown using means, medians, SDs, interquartile ranges, and proportions, as appropriate. We first estimated the effects of various demographic, clinical, and laboratory factors on the prolongation of the QTc interval using univariate analyses. We also fit multivariate logistic and linear models, which included continuous variables for age, SLE disease duration, SLEDAI-2K, SDI, and corrected calcium, potassium, and magnesium levels, as well as dichotomous variables for sex, anti-ENA, CAD risk factors, and drug exposure. We investigated confounding by comparing odds ratios (ORs) for each main variable of interest as possible confounders exited or entered the model. Analyses were performed using SAS software, version 9.2. The study was approved by the institutional ethics boards of the involved clinics and written consent was obtained from each subject according to the Declaration of Helsinki.

RESULTS

Characteristics of the patients. Seven hundred seventy-nine subjects participated in this study. Baseline characteristics of the patients are shown in Table 1. The majority (88.4%) were women, 50.7% were white, 22.9% were Asian, 13.1% were African American, and 9.3% were Hispanic. At assessment, the mean \pm SD age was 35.2 ± 13.8 years and the mean \pm SD lupus disease duration was short, at 10.5 ± 14.5 months, as would be expected with an inception cohort. At the time of the assessment, 47.3% had positive anti-Ro/SSA (52 and/or 60 kd), among which 30.2% were anti-Ro/SSA 52 kd positive, 44.2% were anti-Ro/SSA 60 kd positive, and 27.0% were both anti-Ro/SSA 52 and 60 kd positive. Cardiovascular history and risk factors among the study participants are detailed in Table 2. Thirty-one percent of the patients had hypertension and 14.8% were current smokers. Known CAD and structural heart disease were relatively uncommon in the cohort.

EKG abnormalities. The proportions of patients with various EKG abnormalities are shown in Table 3. Premature atrial and ventricular complexes occurred in 1.15% and 1.40% of the patients, respectively. Atrial fibrillation and other supraventricular arrhythmias were less frequent (0.13%). Prominent QRS voltages, suggestive of left ventricular hypertrophy, were found in 5.40% of this population of young patients. Among the patients with ventricular conduction disturbances, incomplete bundle branch block was the most frequent abnormality. Nonspecific

ST-T segment occurred in 30.9%. A high prevalence of repolarization abnormalities was found in our population, with 15.3% having prolonged QTc (≥ 440 msec) and 38.1% having increased QTd.

Clinical and laboratory associations. Table 4 compares the rate of repolarization abnormalities among the various Ro/SSA subgroups (Ro/SSA negative, Ro/SSA 52 kd positive, Ro/SSA 60 kd positive, Ro/SSA 52 kd and/or 60 kd positive, and both Ro/SSA 52 kd and 60 kd positive). Although the mean QTc and the proportion of patients with QTc ≥ 440 msec were slightly higher in Ro/SSA-positive groups compared to the Ro/SSA-negative group, wide confidence intervals (CIs) preclude definitive conclusions.

In univariate and multivariate analyses, anti-Ro/SSA

| Table 1. Characteristics of the patients* | |
|-------------------------------------------|--------------------|
| | Value (n = 779) |
| Age, mean \pm SD years | 35.2 \pm 13.8 |
| Female sex | 88.4 |
| Ethnicity | |
| White | 50.7 |
| Asian | 22.9 |
| African American | 13.1 |
| Hispanic | 9.3 |
| Other | 4.0 |
| Disease duration, mean \pm SD months | 10.5 \pm 14.5 |
| SLEDAI-2K score, mean \pm SD | 5.4 \pm 5.6 |
| Current nephrotic syndrome | 5.2 |
| Active nephritis | 18.7 |
| Current hemodialysis | 0.7 |
| SDI score, mean \pm SD | 0.5 \pm 1.0 |
| Antibodies | |
| Anti-Ro/SSA (52 kd and/or 60 kd) | 47.3 |
| Anti-La/SSB | 20.2 |
| Anti-Sm | 30.6 |
| Anti-RNP | 12.4 |
| Anti-DNA | 43.9 |
| Medications, current use† | |
| NSAIDs | 20.8 |
| Antimalarials | 68.4 |
| Immunosuppressants | 38.1 |
| Steroids | 66.7 |
| Aspirin | 16.2 |
| Anticoagulants | 5.5 |
| Antihypertensives | 31.0 |
| Oral contraceptives | 11.1 |
| Hormone therapy | 3.6 |
| Low potassium level‡ | 10.9 |
| Low magnesium level§ | 15.2 |
| Low calcium level¶ | 13.3 |

* Values are the percentage unless indicated otherwise. SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NSAIDs = non-steroidal antiinflammatory drugs.
† No patients were using antipsychotics, human immunodeficiency virus protease inhibitors, or cocaine.
‡ Defined as ≤ 3.4 mmoles/liter.
§ Defined as ≤ 0.74 mmoles/liter.
¶ Defined as ≤ 2.10 mmoles/liter.

Table 2. Cardiovascular status among study participants

| | Study participants (n = 779) |
|----------------------------------------------------|---------------------------------|
| Current smokers, no. (%) | 115 (14.8) |
| Alcohol consumption, mean \pm SD per week | 1.0 \pm 3.3 |
| Body mass index, mean \pm SD kg/m ² | 25.1 \pm 6.3 |
| Hypertension, no. (%)* | 212 (31.0) |
| Diabetes mellitus, no. (%) | 20 (2.6) |
| High-sensitivity C-reactive protein, mean \pm SD | 4.9 \pm 13.8 |

* Data on the total population were not available and the denominator is slightly less than 779.

antibodies, for any subtype, were not associated with QTc prolongation (Table 5) or increase in QTd (Table 6). Similarly, there was no effect of anti-Ro/SSA level on these parameters (data not shown).

Other variables. In univariate analysis, the following variables were associated with QTc prolongation and showed a stronger association for higher QTc cut points: antihypertensive drug (ORs 2.10 [95% CI 1.34, 3.29] to 7.22 [95% CI 1.44, 36.11]) and age (ORs 1.02 [95% CI 1.01, 1.04] to 1.07 [95% CI 1.02, 1.12]), depending on the QTc thresholds. Because of the small numbers, we were unable to demonstrate if any specific antihypertensive medication

Table 3. Electrocardiographic abnormalities*

| | Value (n = 779) |
|-----------------------------------------------------------------|--------------------|
| Supraventricular arrhythmias | |
| Premature atrial complexes | 1.15 |
| Atrial fibrillation | 0.13 |
| Atrial flutter/supraventricular tachycardia/wandering pacemaker | 0 |
| Premature ventricular contractions | 1.40 |
| Atrioventricular heart block | 0.64 |
| Left ventricular hypertrophy | 5.4 |
| Right ventricular hypertrophy | 0.1 |
| Ventricular conduction disturbances | |
| Incomplete bundle branch block | 2.68 |
| Right bundle branch block | 0.77 |
| Left bundle branch block | 0.26 |
| Left anterior fascicular block | 0.38 |
| Left posterior fascicular block | 0 |
| ST segment changes | |
| Nonspecific | 30.9 |
| Compatible with myocardial infarction | 1.83 |
| QTc, mean \pm SD msec | 415.3 \pm 25.7 |
| Increased QTc (≥ 440 msec) | 15.3 |
| Increased QTc (≥ 460 msec) | 5.3 |
| QTd, mean \pm SD msec | 34.2 \pm 14.7 |
| Increased QTd (≥ 40 msec) | 38.1 |

* Values are the percentage unless indicated otherwise. All atrioventricular heart blocks were first-degree blocks. QTc = corrected QT interval; QTd = QT dispersion.

Table 4. QT characteristics among systemic lupus erythematosus patients with various Ro/SSA positivity statuses*

| | Ro/SSA negative (n = 314) | Ro/SSA 52 kd positive (n = 180) | Ro/SSA 60 kd positive (n = 264) | Ro/SSA 52 kd and/or 60 kd positive (n = 283) | Ro/SSA 52 kd and Ro 60 kd positive (n = 161) |
|----------------------------|------------------------------|------------------------------------|------------------------------------|-------------------------------------------------|-------------------------------------------------|
| QTc, mean ± SD msec | 413.5 ± 26.5 | 416.7 ± 24.9 | 415.5 ± 24.4 | 415.9 ± 24.6 | 416.2 ± 24.6 |
| QTc minimum, msec | 343 | 352 | 352 | 352 | 352 |
| QTc maximum, msec | 562 | 488 | 488 | 488 | 488 |
| Increased QTc, % ≥440 msec | 12.4 | 17.8 | 16.7 | 17.0 | 17.4 |
| Increased QTc, % ≥460 msec | 5.7 | 5 | 3.8 | 4.6 | 3.7 |
| QTd, mean ± SD msec | 32.4 ± 14.8 | 33.2 ± 16.2 | 33.9 ± 16.1 | 34.1 ± 16.3 | 32.8 ± 15.8 |
| Increased QTd, % ≥40 msec | 37.6 | 38.2 | 40.8 | 40.9 | 37.7 |

* Complete anti-Ro/SSA serologies (52 and 60 kd) were available for 597 patients. QTc = corrected QT interval; QTd = QT dispersion.

was associated with increased QTc intervals. Some variables showed an association only at certain QTc cut points: thyroid replacement therapy (OR 2.45 [95% CI 1.38, 4.36]) at a cutoff of ≥440 msec and total SDI (OR 1.38 [95% CI 1.06, 1.79] at ≥440 msec and OR 1.39 [95% CI 1.03, 1.87] at ≥450 msec).

Contribution of the variables to multivariate models has been assessed and, with the exception of antihypertensive drugs and increasing age, we were unable to determine if any clinical or laboratory factors were associated with prolonged QTc or QTd (Table 5). In particular, although the CIs were large, neither the level of electrolytes (potassium, magnesium, or corrected calcium) nor the presence of any antibodies was found to impact QTc interval duration or QTd.

DISCUSSION

Our study is by far the largest to date evaluating EKG abnormalities and more specifically, the relationship between anti-Ro/SSA and repolarization abnormalities in SLE patients. Although many patients in our cohort were young (mean age 35.2 years) and had a short disease duration (mean 10.5 months), a considerable number of pa-

tients in the SLICC cohort already demonstrated evidence of cardiac abnormalities by EKG. In data from a healthy population of women ages 25–44 years (15), the mean prevalence of most EKG abnormalities has been reported to be relatively low: 0.1% atrioventricular block, 0.2% bundle branch block, 0.04% atrial fibrillation or flutter, and 0.1% QRS voltage criteria indicative of left ventricular hypertrophy. However, our cohort was not restricted to women and also included subjects older than the age range 25–44 years. However, analyzing the sample of women ages 25–44 years from our cohort, the mean prevalence of most EKG abnormalities remains high, at 0.85% atrioventricular block, 4.79% bundle branch block, and 4.2% left ventricular hypertrophy, although atrial fibrillation or flutter was not seen in this subpopulation. Abnormalities such as conduction defects may represent sequelae of past or active lupus myocarditis (16) and could also be related to the high rate of CAD risk factors such as hypertension in our patients, although SLE itself carries an independent risk for CAD even after adjustment for traditional Framingham risk factors (17).

Although a substantial proportion of patients in our cohort manifested repolarization abnormalities such as prolonged QTc (15.3%) and increased QTd (38.1%), se-

Table 5. Multivariate analyses for QTc as a continuous variable and for different QTc thresholds*

| | QTc | QTc ≥440 msec | QTc ≥450 msec | QTc ≥460 msec | QTc ≥480 msec |
|------------------------------------|---------------------|--------------------|--------------------|--------------------|---------------------|
| Age | 0.33 (0.17, 0.49)† | 1.01 (0.99, 1.03) | 1.03 (1.01, 1.05)† | 1.04 (1.01, 1.06)† | 1.07 (1.02, 1.12)† |
| Antihypertensive | 5.93 (1.20, 10.70)† | 1.90 (1.57, 3.11)† | 2.62 (1.43, 4.80)† | 3.26 (1.49, 7.15)† | 5.91 (1.15, 30.16)† |
| Ro/SSA 52 kd positive | 3.33 (−1.35, 8.00) | 1.45 (0.88, 2.41) | 1.60 (0.85, 3.00) | 0.95 (0.43, 2.10) | 0.93 (0.18, 4.84) |
| Ro/SSA 60 kd positive | 1.47 (−2.66, 5.6) | 1.36 (0.86, 2.30) | 1.25 (0.71, 2.20) | 0.48 (0.21, 1.13) | 0.50 (0.10, 2.62) |
| Ro/SSA 52 kd and/or 60 kd positive | 2.25 (−1.87, 6.34) | 1.32 (0.81, 2.12) | 1.51 (0.86, 2.67) | 0.64 (0.28, 1.43) | 0.44 (0.09, 2.30) |
| Ro/SSA 52 kd and 60 kd positive | 2.72 (−2.08, 7.53) | 1.37 (0.82, 2.30) | 1.32 (0.72, 2.42) | 0.64 (0.26, 1.59) | 1.09 (0.21, 5.67) |

* Values are the odds ratio (95% confidence interval) from multivariate analysis, except for the first column, where they are the regression coefficient (95% confidence interval) from linear regression models. Variables not appearing in the table were removed from the final model because they were not predictive of the outcome nor they were confounders. The small number of patients (n = 2) with QTc ≥500 msec precludes multivariate analysis at this threshold. QTc = corrected QT interval.
† Significant.

Table 6. Multivariate analyses for QTd*

| | QTd | QTd ≥ 40 msec |
|------------------------------------|---------------------|--------------------|
| Age | 0.09 (−0.01, 0.18) | 1.01 (0.99, 1.02) |
| Ro/SSA 52 kd positive | −0.01 (−2.78, 2.76) | 0.94 (0.65, 1.35) |
| Ro/SSA 60 kd positive | 1.30 (−1.26, 3.86) | 1.13 (0.80, 1.58) |
| Ro/SSA 52 kd and/or 60 kd positive | 1.68 (−0.86, 4.22) | 1.14 (0.82, 1.6) |
| Ro/SSA 52 kd and 60 kd positive | −0.54 (−3.41, 2.32) | 0.92 (0.63, 1.34) |

* Values are the regression coefficient (95% confidence interval) from linear regression models for QTd and the odds ratio (95% confidence interval) from logistic regression models for QTd ≥ 40 msec. Variables not shown in the table were removed from the final model because they were not predictive of the outcome nor they were confounders. QTd = QT dispersion.

vere abnormalities were rare (<1% with QTc ≥ 550 msec). QTc prolongation is an independent risk factor for the development of complex ventricular arrhythmias, and rarely, sudden death (1,2). Increased QTd is another indicator of myocardial electrical instability that has been associated with arrhythmias and cardiac death (18). In general medical populations, QTd is an independent predictor of cardiovascular mortality (hazard ratio 1.28 [95% CI 1.01, 1.60] per each 10-msec increase in QTd) (19). In patients with rheumatic diseases, a 50-msec increase in the QTc interval has been associated with a doubling of the relative hazard for all-cause mortality, and some authors have suggested a connection between disease activity and arrhythmogenesis (20). Important associations of repolarization abnormalities in our study included age and anti-hypertensive therapy, which is not surprising, since both have been associated with prolonged QTc (21–23). Wide CIs precluded definitive conclusions for other clinical and laboratory variables in our study, although numerical increases in the QTc interval were observed with anti-Ro/SSA antibody positivity.

Because of their recognized arrhythmogenic effect on the fetal heart, anti-Ro/SSA antibodies have been examined as potential determinants of QTc prolongation in adults with connective tissue diseases (CTDs). The pathogenic role of anti-Ro/SSA and anti-La/SSB antibodies in neonatal lupus is universally accepted, although the exact mechanisms of injury have not been completely clarified. In vivo and in vitro evidence supports a pathologic cascade involving cardiomyocytes apoptosis, binding of maternal antibodies, inflammation, and subsequent replacement of inflamed tissue with fibrosis (24–27). Inhibition of L-type and T-type calcium channels also seems to play an important role (28). However, these mechanisms, which generally lead to irreversible conduction abnormalities, would not explain the reversible changes that are hypothesized to occur in adult patients. Indeed, some evidence, such as the concomitant disappearance of QTc abnormal-

ities and acquired maternal autoantibodies during the first year of life (29), suggests that anti-Ro/SSA antibodies may cause a direct reversible arrhythmogenic effect on ventricular repolarization. However, the pathophysiology underlying QTc prolongation seems to be different from the one involved in neonatal cardiac block, and evidence suggests an inhibitory activity of these autoantibodies on the potassium currents, resulting in an impairment of the ventricular repolarization (30).

In patients with various types of CTD, Lazzerini and colleagues showed statistically significant prolongation of the QTc interval in anti-Ro/SSA-positive adults compared to anti-Ro/SSA-negative adults (4,5,31). Our previous single-center study, performed on a large group of SLE patients with a mean age of 44.8 years and a mean disease duration of 12.9 years, also demonstrated an association between anti-Ro/SSA antibodies and QTc interval prolongation (3). In the current study, although the proportion of patients with prolonged QTc was slightly higher in anti-Ro/SSA-positive groups compared to the anti-Ro/SSA-negative group, CIs were wide and included both important effects and the null value, and therefore were inconclusive. In contrast to a recent study reporting that QTc prolongation was strictly dependent on the anti-Ro/SSA 52-kd level in a population of 49 subjects with various CTDs (5), we did not demonstrate an association between the anti-Ro/SSA specificities or level in our population of 779 SLE patients. Our results are, however, in accordance with previous studies involving a majority of SLE patients who did not demonstrate differences in QTc duration or QTd between anti-Ro/SSA-positive and anti-Ro/SSA-negative patients (7,8,32). It has been proposed previously that SLE patients may have a peculiar resistance to the hypothesized electrophysiologic effects of anti-Ro/SSA antibodies as compared with patients with other CTDs (33). It may also be possible that our lack of ability to show an effect was because of the young age and short disease duration of the patients in our cohort.

Numerous centers around the world participated in our study, and some factors that may impact EKG acquisition (e.g., type of EKG equipment, body position, and fasting state of the participants) were not standardized. However, both EKG interpretation and antibody testing were performed with highly robust methods in a single center. Because no association was found between antiphospholipid antibodies and EKG abnormalities in previous studies, we did not test for these autoantibodies (3). Other potential limitations of the present study include the use of resting 12-lead EKGs rather than 24-hour EKG monitoring (Holter), which can measure diurnal variations of EKG intervals. However, it has been previously shown that QTc prolongation, when present, persists for most of the 24-hour observation period (31). For those lacking computer-generated QTc (21.8% of the participants), the median raw QT was used to derive the Bazett QTc interval, which overcorrects at high heart rates and undercorrects at low heart rates (13). This could contribute to the null effect of our study. Since the threshold at which QTc duration should be considered abnormal also has been a matter of

debate for many years (34,35), we used different cutoffs in our analysis, from 440 msec to 500 msec.

In conclusion, we demonstrated a relatively high prevalence of EKG abnormalities, including repolarization abnormalities, in this inception cohort, although severe abnormalities were rare.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Pineau had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bourré-Tessier, Urowitz, Bernatsky, Huynh, Hanly, Wallace, Gordon, Rahman, Gladman, Fortin, Merrill, Steinsson, Bruce, Ginzler, Dooley, Nived, Sturfelt, Zoma, Pineau.

Acquisition of data. Bourré-Tessier, Urowitz, Clarke, Bernatsky, Krantz, Huynh, Bae, Hanly, Wallace, Gordon, Isenberg, Rahman, Gladman, Fortin, Merrill, Romero-Diaz, Sanchez-Guerrero, Fessler, Alarcón, Steinsson, Bruce, Ginzler, Dooley, Nived, Sturfelt, Kalunian, Ramos-Casals, Petri, Zoma, Pineau.

Analysis and interpretation of data. Bourré-Tessier, Bernatsky, Krantz, Joseph, Belisle, Wallace, Gordon, Isenberg, Gladman, Fortin, Romero-Diaz, Bruce, Nived, Sturfelt, Pineau.

REFERENCES

- Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol* 1993;72:23B–5B.
- Surawicz B. The QT interval and cardiac arrhythmias. *Annu Rev Med* 1987;38:81–90.
- Bourre-Tessier J, Clarke AE, Huynh T, Bernatsky S, Joseph L, Belisle P, et al. Prolonged corrected QT interval in anti-Ro/SSA-positive adults with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2011;63:1031–7.
- Lazzerini PE, Acampa M, Guideri F, Capecchi L, Campanella V, Morozzi G, et al. Prolongation of the corrected QT interval in adult patients with anti-Ro/SSA-positive connective tissue diseases. *Arthritis Rheum* 2004;50:1248–52.
- Lazzerini PE, Capecchi PL, Acampa M, Morozzi G, Bellisai F, Bacarelli MR, et al. Anti-Ro/SSA-associated corrected QT interval prolongation in adults: the role of antibody level and specificity. *Arthritis Care Res (Hoboken)* 2011;63:1463–70.
- Jaeggi ET, Silverman ED, Laskin C, Kingdom J, Golding F, Weber R. Prolongation of the atrioventricular conduction in fetuses exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies did not predict progressive heart block: a prospective observational study on the effects of maternal antibodies on 165 fetuses. *J Am Coll Cardiol* 2011;57:1487–92.
- Gordon PA, Rosenthal E, Khamashta MA, Hughes GR. Absence of conduction defects in the electrocardiograms [correction of echocardiograms] of mothers with children with congenital complete heart block. *J Rheumatol* 2001;28:366–9.
- Costedoat-Chalumeau N, Amoura Z, Hulot JS, Ghillani P, Lechat P, Funck-Brentano C, et al. Corrected QT interval in anti-SSA-positive adults with connective tissue disease: comment on the article by Lazzerini et al [letter]. *Arthritis Rheum* 2005;52:676–7.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang DH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992;35:630–40.
- Gladman DD, Urowitz MB, Goldsmith CH, Fortin P, Ginzler E, Gordon C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997;40:809–13.
- U.S. Food and Drug Administration. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville (MD): Center for Drug Evaluation and Research; 2005.
- Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–70.
- Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT interval dispersion. *Pharmacotherapy* 2005;25:1523–9.
- De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. *Heart* 2000;84:625–33.
- Mandell BF. Cardiovascular involvement in systemic lupus erythematosus. *Semin Arthritis Rheum* 1987;17:126–41.
- Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331–7.
- Kautzner J, Malik M. QT interval dispersion and its clinical utility. *Pacing Clin Electrophysiol* 1997;20:2625–40.
- Salles GF, Deccache W, Cardoso CR. Usefulness of QT-interval parameters for cardiovascular risk stratification in type 2 diabetic patients with arterial hypertension. *J Hum Hypertens* 2005;19:241–9.
- Panoulas VF, Toms TE, Douglas K, Sandoo A, Metsios GS, Stavropoulos-Kalinoglou A, et al. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden. *Rheumatology (Oxford)* 2014;53:131–7.
- Mangoni A, Kinirons M, Swift C, Jackson S. Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis. *Age Ageing* 2003;32:326–31.
- Festa A, D'Agostino R, Rautaharju P, Mykkanen L, Haffner SM. Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. *Am J Cardiol* 2000;86:1117–22.
- Brown DW, Giles WH, Greenlund KJ, Valdez R, Croft JB. Impaired fasting glucose, diabetes mellitus, and cardiovascular disease risk factors are associated with prolonged QTc duration: results from the Third National Health and Nutrition Survey. *J Cardiovasc Risk* 2001;8:227–33.
- Clancy RM, Neufing PJ, Zheng P, O'Mahony M, Nimmerjahn F, Gordon TP, et al. Impaired clearance of apoptotic cardiocytes is linked to anti-SSA/Ro and -SSB/La antibodies in the pathogenesis of congenital heart block. *J Clin Invest* 2006;116:2413–22.
- Schmidt KG, Ulmer HE, Silverman NH, Kleinman CS, Copel JA. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. *J Am Coll Cardiol* 1991;17:1360–6.
- Nield LE, Silverman ED, Taylor GP, Smallhorn JF, Mullen JB, Silverman NH, et al. Maternal anti-Ro and anti-La antibody-associated endocardial fibroelastosis. *Circulation* 2002;105:843–8.
- Buyon JP, Clancy RM. Neonatal lupus: basic research and clinical perspectives. *Rheum Dis Clin North Am* 2005;31:299–313.
- Xiao G, Hu K, Boutjdir M. Direct inhibition of expressed cardiac L- and T-type calcium channels by IgG from mothers whose children have congenital heart block. *Circulation* 2001;103:1599–604.
- Cimaz R, Meroni PL, Brucato A, Fesstova V, Panzeri P, Golene K, et al. Concomitant disappearance of electrocardiographic abnormalities and of acquired maternal autoantibodies during the first year of life in infants who had QT interval prolongation and anti-SSA/Ro positivity without congenital heart block at birth. *Arthritis Rheum* 2003;48:266–8.
- Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. *Europace* 2008;10:1133–7.
- Lazzerini PE, Capecchi PL, Guideri F, Bellisai F, Selvi E,

-
- Acampa M, et al. Comparison of frequency of complex ventricular arrhythmias in patients with positive versus negative anti-Ro/SSA and connective tissue disease. *Am J Cardiol* 2007;100:1029–34.
32. Yavuz B, Atalar E, Karadag O, Tulumen E, Ozer N, Akdogan A, et al. QT dispersion increases in patients with systemic lupus erythematosus. *Clin Rheumatol* 2007;26:376–9.
33. Lazzerini PE, Capecchi PL, Acampa M, Selvi E, Guideri F, Bisogno S, et al. Arrhythmogenic effects of anti-Ro/SSA antibodies on the adult heart: more than expected? *Autoimmun Rev* 2009;9:40–4.
34. Johnson JN, Ackerman MJ. QTc: how long is too long? *Br J Sports Med* 2009;43:657–62.
35. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2010;55:934–47.
-

DOI 10.1002/acr.22524

Erratum

In the article by Humphreys et al in the September 2014 issue of *Arthritis Care & Research* (pages 1296–1301) an error was detected in the Results. On page 1298, the sentence beginning “Overall, persistently increasing, but stable mortality rates . . .” should have read “Overall, persistently increased, but stable mortality rates over time were seen in patients with RA, when modeled by calendar year.”

We regret the error.