Assessing QT interval in patients with autoimmune chronic inflammatory diseases: perils and pitfalls

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The QT interval on the ECG reflects the duration of action potential (AP) in ventricular cardiomyocytes, in turn representing the sum of ventricular depolarisation and repolarisation. AP is caused by transmembrane flow of ions, including inward depolarising currents mainly through sodium and calcium channels, that is, the sodium current (INa) and the L(long-lasting)-type calcium current (ICaL), and outward repolarising currents mainly through potassium channels, particularly the transient outward current (Ito), the rapid and the slow component of the delayed rectifier potassium current (rapid component, IKr, and slow component, IKs) and the inward rectifier potassium current (IK1) (figure 1).

The long QT syndrome (LQTS) is a multifactorial disorder characterised by a prolonged heart rate-corrected QT interval (QTc), which predisposes to life-threatening ventricular arrhythmias, particularly torsades de pointes (TdP), that can degenerate into ventricular fibrillation and cause sudden cardiac death. Although there is no threshold of QTc prolongation at which TdP is certain to occur, the risk of TdP gradually increases as the QTc prolongs over 440 ms, with an approximately 5%–7% exponential increase in risk for each 10 ms prolongation of QTc. In particular, studies indicate that a QTc>500 ms is associated with a twofold to threefold higher risk for TdP.

The LQTS is traditionally classified as congenital or acquired, even though it has become clear how in many cases the clinical phenotype is the result of a complex interaction of multiple aetiological factors operating concomitantly in the single patient. Congenital LQTS is caused by genetically determined abnormalities affecting directly or indirectly the function of specific ionic channels involved in ventricular AP, that is, potassium (loss of function), sodium or calcium channels (gain of function). To date, over 1000 mutations in 15 LQTS-susceptibility genes have been identified. Acquired LQTS is much more prevalent than the congenital form, in most cases representing an adverse effect of drugs or the result of electrolyte disturbances interfering with cardiomyocyte electrophysiology. In particular, molecular basis of drug-induced LQTS almost exclusively involves the reduction of IKr through hERG-potassium channel blockade.

Other currently recognised causes of acquired LQTS include structural heart diseases, bradycardia, endocrine disorders, liver diseases, nervous system injuries, HIV infection, starvation, hypothermia and toxins.

Recently, a number of basic and clinical studies strongly suggest that inflammation and immunity represent further important determinants of acquired LQTS.

Accumulating evidence indicates that inflammatory activation profoundly impacts the electrophysiological properties of cardiomyocytes via multiple effects, ultimately resulting in a prolongation of AP duration (APD), and thereby QTc. In this scenario, the key mediators seem to be the inflammatory cytokines (particularly tumour necrosis factor-α, interleukin (IL)-6, IL-1β) which may affect myocardium either directly, by modulating the expression and function of specific ion channels critically involved in AP (figure 1) or indirectly, by increasing central nervous system sympathetic drive on the heart. Among systemic autoimmune diseases (ADs), the largest evidence has been reported for rheumatoid arthritis (RA) and connective tissue diseases (CTDs). Recent studies demonstrated that QTc is frequently prolonged in RA, associates with disease severity and inflammatory markers and independently predicts all-cause mortality. Notably, in these patients QTc duration correlated with circulating levels of inflammatory cytokines, and anti-IL-6 therapy with...
tocilizumab resulted in a rapid and significant QTc shortening.\textsuperscript{9} Moreover, marked QTc prolongation/TdP occurrence has been reported in chronic inflammatory arthritis patients with elevated C reactive protein (CRP) and IL-6 levels.\textsuperscript{10} Several studies performed in patients with different CTDs reported a high overall prevalence of QTc prolongation (up to $\sim$30%),\textsuperscript{4} with circulating IL-1β levels independently predicting the presence of a prolonged QTc.\textsuperscript{11} Specifically, patients with SLE display a longer mean QTc than controls, a 7%–15% incidence of QTc prolongation (marked QTc prolongation, ie, $\geq 500$ ms, in $\sim$3%), which is significantly associated with disease activity and overall inflammatory burden.\textsuperscript{4, 12}

Besides inflammatory activation, specific autoantibody-mediated mechanisms may also contribute to QTc prolongation occurring in patients with ADs.\textsuperscript{4} In particular, it has been demonstrated that anti-Ro/SSA antibodies (specifically the anti-Ro/SSA-52kD subtype) are responsible for a novel form of acquired LQTS of autoimmune origin, by directly cross-reacting with the extracellular loop of the hERG-potassium channel pore-forming region, as a result of molecular mimicry mechanisms.\textsuperscript{13} Such an interaction leads to Ik$\text{r}$ inhibition, resulting in APD and QTc prolongation (figure 1). Accordingly, several clinical studies demonstrated that patients with anti-Ro/SSA-positive CTD (and their newborns) frequently display QTc prolongation, which correlated with circulating autoantibody levels and complex ventricular arrhythmias incidence.\textsuperscript{13} Moreover, a high prevalence hERG-binding and Ik$\text{r}$ blocking anti-Ro/SSA-52kD antibodies was also found in a cohort of unselected patients with TdP, in most cases without any history of AD, thus raising the distinct possibility that these autoantibodies may represent a clinically silent novel risk factor for QTc prolongation and TdP in the general population as well.\textsuperscript{15} Despite the fact that most of the data strongly suggest that anti-Ro/SSA-mediated electrophysiological effects have a significant clinical impact, some studies reported partially conflicting results (either slight differences but very close to statistical significance, or no association between anti-Ro/SSA and QTc prolongation), both in adults and in children.\textsuperscript{14} Notably, even among studies showing a significant association, markedly different percentages of QTc prolongation in patients with anti-Ro/SSA-positive CTD were observed (from $\sim$10% to 60%).\textsuperscript{14} Although this QTc variability can be attributed to differences among CTD cohorts in terms of autoantibody concentration and specificity (high levels of anti-Ro/SSA are particularly frequent in Sjögren syndrome, much less in SLE and systemic sclerosis),\textsuperscript{16} it may also be in part explained by electrophysiological considerations. In fact, based on the evidence that (i) besides the hERG-channel, anti-Ro/SSA are able to bind to Ca$^{2+}$-channels (L-type and T-type) and inhibit related currents\textsuperscript{17} and (ii) Ca$^{2+}$-channels and K$^+$-channels have opposing effects on APD (figure 1), it is conceivable that a concomitant inhibitory effect of anti-Ro/SSA on Ca$^{2+}$-channels can partially counteract Ik$\text{r}$ inhibition-dependent APD prolongation in vivo, thus reducing the extent of QTc prolongation observed. On the basis of this hypothesis, recently confirmed by mathematical simulation data,\textsuperscript{18} intrinsic (inherited or acquired) differences in K$^+$-channel and Ca$^{2+}$-channel expression (ion channel reserves) on patients’ cardiomyocytes may also contribute to the QTc variability observed.\textsuperscript{19, 20}

In a recent publication in Lupus Science and Medicine, Geraldino-Parrilla \textit{et al}\textsuperscript{21} analysed ECG repolarisation parameters in a cross-sectional study involving 189 patients with autoimmune chronic inflammatory
diseases, 50 affected with SLE and 139 with RA. The authors reported that non-specific ST-T abnormalities were significantly more common (~fivefold), and mean QTC significantly longer (~25 ms) in SLE when compared with patients with RA. Since RA is associated with a similarly increased cardiovascular risk, thus representing a good control group for patients with SLE, the authors concluded that the different prevalence of repolarisation alterations observed between the two populations is a robust finding. The risk of presenting non-specific ST-T abnormalities increased with older age in patients with SLE, while was associated with male sex in patients with RA. As regards QTC duration, status use was inversely associated with this parameter in patients with SLE, while in the RA group female sex, CRP levels and disease activity measured by disease activity score (DAS)-28 were associated with an increased QTC length.

Although the authors try to further corroborate their conclusions by adjusting data for confounders, nevertheless it should be stressed that the two groups analysed are too different, thus rising concerns about the actual significance of the results, particularly QT interval findings. In fact, while an increased prevalence of non-specific ST-T abnormalities was found in patients with SLE despite the presence of a ‘favourable’ matching (patients with SLE were younger, predominantly females and with shorter disease duration than patients with RA) thus supporting the validity of these findings, this consideration is not true for the QTC, whose assessment may not be true for the QTc, whose assessment may be significantly lower, approximately two times than patients with SLE. Moreover, in a previous study demonstrating high prevalence of QTC prolongation in patients with RA, severe disease activity was present in most patients (65%; mean DAS28-erythrocyte sedimentation rate (ESR): 5.1; median IL-6 levels ∼10 pg/mL), approximately three times lower when compared with those found in a large French cohort of high disease activity patients with RA (median DAS28-erythrocyte sedimentation rate (ESR): 5.1; median IL-6 levels 3.8 corresponded to low disease activity.23 Accordingly, in this RA cohort, median CRP levels were 2.1 mg/L (ie, 0.21 mg/dL, a value below the cut-off of 1 mg/dL recently selected by ACR/European League Against Rheumatism to define remission).24 Indeed, also IL-6 levels in this RA cohort were rather low (median 3.6 pg/mL), approximately seven times higher than in the present RA cohort (1.5 mg/dL, ie, 15 mg/L).9

Second, the specific autoantibody profile of patients with AD under study has to be carefully characterised, particularly the presence, subtype and titre of anti-Ro/SSA antibodies.

In the present study, the authors found no association between anti-Ro/SSA positivity and QTC length in patients with SLE, thereby concluding that these autoantibodies do not contribute to the pathogenesis of the QTC prolongation observed. However, they neither analysed anti-Ro/SSA subtypes nor their circulating levels, both representing critical factors for the clinical appearance of anti-Ro/SSA-associated QTc prolongation. In fact, it has been demonstrated that the anti-Ro/SSA-52kD subtype only can inhibit the IKr current,13 15 and that high anti-Ro/SSA-52kD levels are required for developing QTc prolongation in positive patients, at least 10 times higher than the upper normal limit.26 Thus, it is possible that in this SLE cohort prevalence and/or circulating levels of the anti-Ro/SSA-52kD subtype were too low to produce a clinically evident QTc prolongation. Notably, a very recent paper27 identified Tpeak-Tend (Tp-e) interval as a better ECG predictor of anti-Ro/SSA-52kD-associated ventricular repolarisation abnormalities in positive patients. Indeed, IKr current is activated after the peak of T wave (figure 1). Thus, Tp-e may be more sensitive than QTc to detect the electrophysiological consequences of anti-Ro/SSA-52kD-associated hERG-channel inhibition in the clinical setting.

The potential impact of demography on QTc findings represents another important factor that cannot be disregarded in this type of study. Indeed, it is well recognised that gender and ethnic characteristic markedly impact on the epidemiology of ADs in general, of SLE and RA in particular.28
However, the two groups of patients studied by Geraldino-Parrilla et al. are very different, maybe too much, in terms of sex and ethnicity, and this could have significantly biased the results. In particular, in the general population it is well-established that female sex is associated with longer QTc duration (accordingly QTc prolongation cut-offs are different in males vs females) and higher TdP risk, via complex effects of sexual hormones on cardiac ion currents. Thus, the longer QTc duration observed in patients with SLE versus patients with RA may be influenced by the higher percentage of females in the SLE group (92% vs 61%; p<0.0001). Accordingly, in the RA cohort QTc duration correlated with female sex (in the SLE cohort, the large preponderance of females probably did not allow to evaluate the weight of the gender on QTc). Moreover, also ethnicity is very different between the two groups. Indeed, RA cohort mainly consisted of whites (87%), while patients with SLE were in the large majority (96%) Hispanic or blacks (74% and 22%, respectively). Many large studies involving both general population patients and patients with cardiac diseases found that in blacks and Hispanics the QTc interval is longer than in whites. As a result, higher percentages of females and Hispanic/blacks may have also contributed to the longer QTc observed in the SLE cohort when compared with patients with RA.

In conclusion, cardiovascular involvement is currently recognised as a main cause of morbidity and mortality in autoimmune chronic inflammatory diseases. In this context, growing recent evidence indicates inflammation and autoimmunity as novel cardiovascular risk factors functionally impacting ventricular repolarisation, particularly promoting QTc prolongation and associated life-threatening arrhythmias. If on one hand these considerations fully justify the increasing attention that this ECG parameter is receiving in these patients, on the other hand it is essential that researchers are alerted on the specific perils of this type of study in order to avoid methodological pitfalls when assessing QT interval in a population with many peculiarities such as the patients with AD.

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