Arrhythmias in systemic lupus erythematosus
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ABSTRACT
Cardiac involvement is present in more than half of the patients with Systemic Lupus Erythematosus (SLE). However, studies on the prevalence of arrhythmias in this disease and laboratorial correlations predictive of their development do not exist. It seems possible that the classic second mortality peak is related to arrhythmias, mainly due to the sudden nature of those deaths. Autoimmune process, atherosclerotic complications, and even adverse effects secondary to the treatment of this disorder (chloroquine cardiotoxicity) seem to be the main pathophysiological mechanisms of those disturbances. The direct participation of autoantibodies, such as anti-Ro/SSA and anti-RNP, is still controversial. All types of AV blocks (AVB), intraventricular conduction disturbances, and sick sinus syndrome have already been described in this disease. Tachycardias identified more often include sinus tachycardia, atrial fibrillation, and atrial ectopies. Long QT syndrome and the presence of late potentials in signal-averaged ECG have also been described in SLE patients and they can be associated with increased mortality rates. Cardiac toxicity secondary to chloroquine could be responsible for several types of arrhythmias. However, few cases of fascicular block evolving to complete AV block have been described. Since these adverse effects are rarely reported, the beneficial anti-inflammatory and immune properties support the use of antimalarials in this disease. A complete cardiologic evaluation should include the conduction system and must be carried out in all SLE patients to identify arrhythmias, therefore preventing symptoms and also sudden cardiac death.

Keywords: systemic lupus erythematosus, cardiac arrhythmias, conduction system, antimalarial, electrocardiogram.

INTRODUCTION
Arrhythmias and conduction system disorders are among the cardiovascular disturbances caused by systemic lupus erythematosus (SLE). Immuno-mediated damage, atherosclerotic complications, or even adverse effect of the treatment (chloroquine-induced cardiotoxicity) seem to be the mechanisms involved more often in the pathophysiology of those disturbances. As a rule, the literature has not given proper clinical attention to the development of arrhythmias in those patients. So far, the evidence related to electrocardiographic disturbances is restricted to studies with small number of patients, although cardiac involvement can affect up to 50% of the cases. Based on current knowledge on the electogenesis of arrhythmias and their clinical implications, it can said that the second mortality peak in SLE is related with the development of arrhythmias, especially due to the sudden nature of the deaths reported. In reality, ventricular arrhythmias have received little attention; however, Abu-Shakra et al., in a study with 665 SLE patients, identified sudden death as the fourth more common cause of death along 20 years of follow-up. Besides, Godeau et al. evaluated the relationship between the presence of conduction disruption and mortality. One-hundred and three SLE patients with active disease were evaluated; after a 10-year follow-up, conduction disturbances were present in 17.5% of the patients, and their mortality rate was significantly higher when compared to patients with normal ECG. Finally, a Chinese study with 566 SLE patients followed-up for more than 30 years identified male gender and electrocardiographic changes as independent risk factors for mortality in this disorder.

Due to the small number of studies in the literature, a consensus on the prevalence of arrhythmias in SLE patients
do not exist and, therefore, laboratorial aspects predictive of those events have not been defined. 10-12 The mechanism of arrhythmias in SLE has not been completely elucidated, and they can be related with the inflammatory process of pericarditis and myocarditis, atherosclerotic myocardial ischemia, or as a consequence of vasculitis of small vessels with collagen and fibrotic deposits that affect the conduction system. 1-3 In fact, clinical myocarditis is identified in 3 to 15% of the cases of SLE, 13 and it can be associated with the presence of anti-Ro/SSA antibodies. 14 This could evolve into progressive ventricular dysfunction, dilated cardiomyopathy, and cardiac failure and, even in the presence of mild clinical manifestation, it should be treated with high doses of corticosteroids and/or immunosuppressors. 15 On the other hand, myocardial involvement could be present even in asymptomatic patients. Myocardial perfusion studies with technetium-99m sestamibi scintigraphy have documented abnormal perfusion in SLE patients, even in the absence of coronary artery obstruction 16. Besides the associations between anti-Ro/SSA and myocarditis described, Logar et al. also observed a relationship with conduction disturbances among 67 SLE patients. 14

The direct participation of specific antibodies, such as anti-Ro/SSA and anti-RNP, is controversial. Studies that observed a significant role of auto-antibodies in patients with brady- or tachyarrhythmias were not specific for SLE. 17,18 Neonatal lupus, a rare syndrome related to transplacental transportation of maternal anti-Ro/SSA and/or anti-La/SSB to the fetus can lead to myocarditis, AVB, and even intrauterine death. 19,20 Neonatal lupus has been identified as the cause of isolated congenital heart block in approximately 60% of those affected due to the identification of maternal anti-Ro/SSA and/or anti-La/SSB. 21 It has also been demonstrated in experimental models that anti-Ro/SSA antibodies of 52kDa are capable of inducing cardiac block. 22 Conduction disruption is commonly permanent and it can be associated with structural cardiac disorders. 23 Sinus bradycardia and prolonged QTc have also been reported in those patients. 24 However, evidence that the development of arrhythmias in adult patients with SLE is similar to the changes observed in neonatal lupus does not exist.

Cardiac arrhythmias and disorders of the conduction system

As for bradycardia, all AVBs, intraventricular conduction defects (IVCD), and sinus node dysfunction (SND) have been described in SLE. 3,25,26 On the other hand, the tachycardias reported more often include sinus tachycardia, atrial fibrillation, and ectopic atrial beats. 11,12 Isolated AVBs have an estimated prevalence of 5%, and 3rd degree AVB seems to be even less common. Autopsies of SLE patients identified fibrosis of the AV node and conduction tissue, periarteritis of nodal arteries, and involvement of the sinus node during active pericarditis as causes of bradycardia. One case of third degree AVB associated with myocarditis and the presence of anti-U1-RNP antibodies has been reported. 27

Increased QT interval is associated with an increase in cardiovascular mortality in different cardiopathies. Evaluating 140 SLE patients and 37 healthy controls, Cardoso et al. 28 evaluated the QT interval corrected for the heart rate by Bazett’s formula (QTc = QT/√RR) and also the QT dispersion (QTd), identifying significantly higher values in SLE (QTc max 427.91 ± 31.53 ms versus 410.05 ± 15.45 ms, P < 0.001 and QTd 52.38 ± 22.21 ms versus 37.12 ± 12.88 ms, P < 0.001). In the same study, patients with abnormal QT also had a higher proportion of other electrocardiographic abnormalities than the control group, besides higher incidence of diabetes mellitus and signs of inflammatory activity. It is important to mention that left ventricular hypertrophy and ST and T wave changes were associated both with prolonged QTc and higher QTd.

Decreased myocardial perfusion, even without clinical manifestations, can be a consequence of direct immunologic aggression. Consequently, multiple small areas of fibrosis can affect ventricular repolarization whose electrocardiographic expression can be the first sign of a cardiac problem. The presence of late potentials related to those histopathological changes associated with abnormalities of the autonomic tone can increase the risk of malignant ventricular arrhythmias. An increase in sympathetic activity has been identified in SLE patients, since they have a reduction in heart rate variability. 18

Changes in autonomic tone of varying degrees can be related with the interaction between anti-Ro/SSA antibodies and muscarinic receptors. 29 In this context, abnormalities in ventricular repolarization (QTc and QTd) could predispose patients to malignant arrhythmias.

In a study with adult patients with SLE, Sjögren’s syndrome, and systemic sclerosis with anti-Ro/SSA antibodies (n = 31), Lazzerini et al. 13 observed significantly longer QTc (> 440 ms) than in patients without those antibodies. However, the mechanism by which antibodies would be related with ventricular repolarization changes was not completely explained. In this study, Lazzerini et al. did not observe differences between groups when analyzing the variation in R-R or in the detection of late ventricular potentials, which were altered in both groups. Since the presence of anti-Ro/SSA was related with a prolonged QTc, its presence in the global context of increased sympathetic activity and higher
Arrhythmias in systemic lupus erythematosus

incidence of late potentials can be a determinant factor for sudden death due to arrhythmia. The presence of late potentials in high-resolution electrocardiogram (ECG-HR) was also documented in the study of Paradiso et al., in which 20% of the patients had this alteration compared with only 5.5% in the control group.

In another study, the same authors evaluated the 24-hour Holter in patients with different connective tissue diseases divided according to the presence or absence of anti-Ro/SSA. Prolonged and persistent QTc was observed during the recording (> 60% of the time), as well as a higher incidence of ventricular arrhythmias in the presence of those auto-antibodies. On the other hand, other studies whose populations were composed mainly by SLE patients, anti-Ro/SSA did not identify the presence of prolonged QTc.

Yavuz et al. evaluated 83 SLE patients and 77 healthy individuals, observing significant longer QTd in SLE (55.22 ± 24.7 ms versus 20.7 ± 5.3 ms, P < 0.001). However, disease duration, presence of inflammatory activity, erythrocyte sedimentation rate (ESR), and use of chloroquine were not correlated with longer QTd.

In a study that investigated the relationship of clinical data with biopsy results in 30 SLE patients, Kong et al. identified four patients with cardiac arrhythmia (two with ventricular ectopy, one with atrial fibrillation, and one with atrial flutter), but a correlation with the presence of heart failure was not observed. However, the authors observed abnormalities in the histopathological study (one pericarditis, two myocarditis, and two left ventricular hypertrophy) in four out of five patients with changes in ventricular repolarization on the ECG.

Guzman et al. identified sinus tachycardia in 50% of the patients in a study with 39 patients with active SLE. Even in the absence of clinical signs like fever, hypovolemia, and heart failure, the incidence of sinus tachycardia was greater in SLE patients than in the general population (13%).

Cardiac changes secondary to chloroquine

The relationship of dose, duration of exposure, and individual or genetic predisposition necessary for the development of clinical and histopathological changes secondary to chloroquine toxicity are unknown.

The diagnosis of chloroquine toxicity can be confirmed by endomyocardial biopsy and ultra-structural study with transmission electron microscopy. Classical findings include vacuolated cells with numerous and enlarged secondary lysosomes with a dense material with lamellar structure, myelin and curvilinear bodies, and disorganized miofibrillar structure.

Necrosis of cardiac myocytes can also be observed. Those changes, found mainly in the cardiac septum, could also affect the cardiac conduction system. Recently, the MRI has proven to be extremely useful in the detection of chloroquine-induced cardiomyopathy, representing an excellent non-invasive option for the diagnosis of this complication. Improvement of the cardiac dysfunction after withdrawal of the drug in patients who developed cardiomyopathy has been reported.

Similar to other drugs, such as amiodarone and chlorpromazine, chloroquine accumulates in lysosomes, causing direct inhibition of its enzymes and increasing lysosomal pH, resulting in the formation of cytoplasmic inclusion bodies. Thus, it can promote a significant reduction in the velocity of the action potential of the cells of the cardiac conduction system, prolonging its duration and increasing the refractory period of Purkinje fibers. For this reason, chloroquine could have antiarrhythmic properties as well as cause the development of severe arrhythmias.

In fact, the pathological role of antimalarials in the development of several electrical disturbances is still controversial. Fascicular blockade that can evolve to 3rd degree AVB and syncope is the most common chloroquine-induced electrocardiographic change observed. In an electrocardiographic evaluation of 279 patients with rheumatoid arthritis treated with antimalarials, Jurik and Møller did not observe higher incidence of pathologically increased PR interval (PRI); however, the duration of the PRI was significantly longer in patients than in healthy individuals. On the other hand, a study with 28 SLE patients designed to assess the safety of chloroquine regarding the development of arrhythmia, conduction disruption, and autonomic dysfunction (HR variability) did not detect significant changes.

Recently, our group evaluated the prevalence of arrhythmias and conduction disorders in SLE to determine the influence of the main factors, such as the use of antimalarials. After analyzing 317 SLE patients, we observed electrocardiographic (ECG) abnormalities in 20.8%, and in the 24-hour Holter, in 85.2% of the patients. Prolonged PR interval was associated with lower use of chloroquine (P = 0.01), less time on chloroquine (P = 0.018), and older age (P = 0.029). Thus, it was demonstrated that antimalarials have a protective effect regarding the elevated prevalence of arrhythmias in SLE, and its anti-arrhythmogenic effects should be better investigated.

Although further studies on the subject are necessary, this could be considered a beneficial effect of antimalarials in SLE. It is interesting that their use in rheumatologic diseases is recognized by its lysosomotropic action, which can reduce the production of proinflammatory cytokines. Besides,
other non-lysosomotropic effects have also been demonstrated, such as inhibition of TNF-α release by macrophages.\textsuperscript{43} Those findings strongly suggest benefits of the use of chloroquine, not only promoting better control of SLE-related dyslipidemia and the disease itself,\textsuperscript{44,45} but also in the cardiac conduction system, which are more important than the potential cardiotoxicity.

Besides, the morbimortality of SLE patients secondary to premature coronary artery disease,\textsuperscript{46,47} especially due to the development of dyslipoproteinemia characteristic of this disorder,\textsuperscript{48,49} is well known. At the same time, it is known that cardiac arrhythmia is the main cause of sudden death in the context of coronary insufficiency, demonstrating the importance or routine risk stratification. Although risk management algorithms of this population do not suggest careful evaluation of conduction system disorders, this should be included along with dyslipidemia.\textsuperscript{50-53}

The search to identify predictive factors of arrhythmia, especially of the conduction system, should be done in every SLE patient and identification of arrhythmias should motivate detailed management to prevent limiting symptoms and sudden death. Tissue aggression secondary to the immunologic reaction, or less commonly secondary to disease treatment, can result in arrhythmias that need specific treatment with drugs, catheter ablation, implantable electronic cardiac devices (pacemakers and defibrillators), or even treatment modification to prevent progressive myocardial dysfunction. On the other hand, despite controversies, the beneficial effects of chloroquine on disease evolution seem to surpass the possibility of toxicity. The use of chloroquine could reduce the inflammatory process and, consequently, the development of arrhythmias.

Therefore, increasing the knowledge on the development of arrhythmias in SLE, identifying parameters related to the development of those electrical disruptions, and defining the role of chloroquine are necessary and are yet to be established.

**REFERENCES**

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