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QT prolongation and variability:

new ECG signs of atrial potentials dispersion before atrial fibrillation onset.

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INTRODUCTION:

Atrial fibrillation (AF) is the most common arrhythmia and it affects both life expectancy and quality of life, with considerable morbidity and mortality; for this reason its prevention and effective treatment are of major importance¹.

AF is a heterogeneous arrhythmia resulting from multiple pathophysiological mechanisms. Three major elements (represented in Coumel's triangle²) are necessary for the onset of AF: an anatomical/electrical substrate, a trigger event and disequilibrium of the autonomic nervous system. Typically, a premature beat in an enlarged atrium with electric, contractile and/or structural remodeling, triggers the arrhythmia in a specific moment of imbalance between vagal and adrenergic tone.^{3,4,5,6,7,8,9,10}

The QT interval is an electrocardiographic measurement that represents ventricular repolarization. It is well known that both long and short QT syndromes are correlated with AF.^{11,12} This association could be explained by the presence of similar ion channels in the atria and the ventricles,¹³ whereby QT interval could presumably be indirectly related to atrial repolarization.¹⁴ Since the action potentials' heterogeneity in the atria is critical for the onset of AF,¹⁵ it is in fact conceivable that it may be represented by dispersion and/or increased variability of the QT interval. The aim of our study was to verify if QT interval variation precedes the onset of AF.

METHODS:

Between June 1, 2016 and April 30, 2017, more than 2,500 Holter monitorings were recorded at our institution. The ARIA recorder (Del Mar Reynolds Medical Inc., Spacelabs Healthcare, Issaquah, WA, USA) with a sampling frequency of 128 Hertz and 8 bit resolution was used. Recordings were analyzed by an experienced operator using Impresario software (Del Mar Reynolds Medical Inc.) from June 1, 2016 to October 10, 2016 while in the period from October, 2016 to April, 31, 2017 Sentinel Software (Del Mar Reynolds Medical Inc.) was employed.

Written informed consent for participation in the study was provided by all patients and the study was approved by the institutional ethic committee and performed according to the principles of the latest Declaration of Helsinki.

All events were manually identified and labeled; criteria to consider a Holter recording eligible for further analysis were: (1) onset of 1 or more episodes of sustained (30 seconds) AF; (2) presence of at least 30 minutes of sinus rhythm before the onset of AF; (3) presence of none or few artifacts in the 5 minutes preceding the onset of AF; (4) well defined T-wave of the 10 beats preceding the onset; and (5) recording lasting more than 18 hours.

We recorded the presence and type of structural heart disease based on medical history, clinical examination, 12-lead resting ECG and echocardiographic data.

For the onset of AF, the triggering supraventricular ectopic beat (TSVEB) was searched. For each TSVEB, the coupling interval (CI), the previous cycle (PC) and the prematurity index (PI) were calculated. PI was defined as the ratio between the two previous measurements (CI/PC).

The recording was then scanned to detect any isolated non-triggering supraventricular ectopic beat (NTSVEB) that had the same CI of the control CPSVI. Non-triggering supraventricular ectopic beats (NTSVEB) were not considered if not preceded by 30 minutes of sinus rhythm. If there was no SVEB with the same CI as the TSVEB, the NTSVEB with the shorter and yet most similar CI was selected. If more than 1 non-triggering SVEB had an identical CI, the NTSVEB with the most similar PC was selected.

Subsequently, mean, standard deviation (SD) and variability (the difference between maximum and minimum) of the QT interval in the previous ten beats were measured, before both TSVEB and NTSVEB.

The $T_{\text{peak}}-T_{\text{end}}$, time from the peak to the end of the T-wave, was also measured, and, together with beat-to-beat QT variability, it was considered as an indicator of action potential dispersion.

Corrected QT (QTc) was calculated through Bazett formula ($QTc = QT/\sqrt{RR}$), after calculating the mean QT interval and RR interval within the previous 10 seconds before the AF trigger and the control NTSVEB.

HRV analysis in frequency domain during the 5 minutes before TSVEB and NTSVEB was used as indicator of autonomic activity in accordance with available guidelines.¹⁶ Low-frequency (LF; from 0.04 to 0.15 Hz), high-frequency (HF; from 0.15 to 0.40 Hz) and the ratio of LF/HF were calculated. The LF and HF were measured in normalized units. Trigger episodes were defined as vagal if HRV analysis showed a LF/HF ratio <1.5 , as opposed to the episodes with a LF/HF ratio ≥ 1.5 which were indicated as adrenergic, instead.

Moreover, in accordance with previous studies,¹⁷ episodes were divided in two groups, according to the pattern of onset. Type I onsets consisted of AF paroxysms with cardiac cycle length variation in the previous 30 seconds ($CLV_{30} \geq 10\%$ (including hereby the short-long sequences); onsets were labeled as type II if the CLV_{30} was less than 10%.

STATISTICAL ANALYSIS:

All the measures are presented as mean \pm standard deviation. The statistical significance of differences among mean values was evaluated using Student's test for paired samples. A P-value <0.05 was statistically significant. Analysis was performed with IBM SPSS Software version 19 (SPSS, Inc., Chicago, IL).

RESULTS:

We analyzed 21 AF triggers in a total of 15 patients (9 men, 6 women). The mean age of the population was 68.8 ± 6.6 ; 11 (73%) had hypertension, 2 (13%) diabetes, 6 (40%) structural cardiomyopathy; 65.4% of patients had an atrial enlargement (Tab. 1).

All AF episodes were paroxysmal.

In the comparison between AF triggers and NTSVEBs (Tab. 2, Fig. 1A), mean QTc was significantly different (470.14 ± 56.76 ms vs 436.67 ± 25.58 ms, P-value = 0.006). In addition, QT variability before AF triggers was significantly higher than that of NTSVEBs (36.86 ± 13.14 vs. 21.14 ± 10.08 ms, P-value <0.001), as well as for QTc variability (41.52 ± 15.81 ms vs. 23.10 ± 11.90 ms, P-value <0.001). Significant differences between the two groups were found in the standard deviation of both the QT interval (11.38 ± 3.73 vs. 7.00 ± 3.42 , P-value <0.001) and the QTc (12.76 ± 4.29 vs 6.86 ± 3.77 , P-value <0.001).

According to HRV, calculated on the 5 minutes before AF onset, 10 triggers (48%) were vagal and 11 (52%) were adrenergic (Tab. 3). No statistically significant differences were found comparing vagal and adrenergic onsets. Analyzing vagal AF onsets and their respective NTSVEBs (Fig. 1B), QT variability before triggers was superior to the one before NTSVEB (35.20 ± 16.48 ms vs 22.70 ± 10.23 ms, P-value = 0.006) and a similar trend emerged for QTc (39.30 ± 18.32 ms vs. 25.60 ± 12.91 ms, P-value = 0.029); QT SD (11.00 ± 4.64 ms vs 7.90 ± 3.81 ms, P-value = 0.026) and QTc SD (12.10 ± 4.99 ms vs 7.00 ± 4.45 ms, P-value = 0.022). When focusing on adrenergic AF (Fig. 1C), mean QTc (477.73 ± 57.50 ms vs. 438.00 ± 28.55 ms, P-value = 0.045), QT variability (38.36 ± 9.79 ms vs 19.73 ± 10.21 ms, P-value = 0.005), QTc variability (43.55 ± 13.72 ms vs. 20.82 ± 11.01 ms, P-value = 0.004) and QTc SD (13.36 ± 3.67 ms vs 6.73 ± 3.26 ms, P-value = 0.04) were higher before the onsets than before their control NTSVEBs.

According to CLV₃₀, 7 (33,3%) AF onsets were labeled as type I and 14 (66,6%) as type II (Tab. 4). No statistically significant differences emerged comparing the two types of onset. Focusing on type I onsets and their respective NTSVEBs (Fig. 1D), TSVEBs reported higher QT variability (36.00 ± 14.36 ms vs 17.00 ± 6.08 ms, P-value = 0.011), QTc variability (42.43 ± 18.54 ms vs 17.71 ± 6.47 ms, P value = 0.010), QT SD (10.71 ± 3.55 ms vs 5.43 ± 1.72 ms, P-value = 0.006) and QTc SD (12.43 ± 4.35 ms vs 5.86 ± 1.77 ms, P-value = 0.005). Comparing type II triggers to their control NTSVEBs (Fig. 1E), QTc average (476.64 ± 59.41 ms vs 438.86 ± 24.35 ms, P-value = 0.029), QT variability (37.29 ± 13.03 ms vs 24.64 ± 12.15 ms, P value = 0.016), QTc variability (41.07 ± 15.00

ms vs 25.79 ± 13.46 ms, P-value = 0.011), QT SD (11.71 ± 3.91 ms vs 7.79 ± 3.83 ms, P-value = 0.013) and QTc SD (12.93 ± 4.41 ms vs 8.29 ± 4.12 ms, P value = 0.009) were significantly higher before the onsets.

DISCUSSION:

Even though AF is the most common arrhythmia, its pathology, due the several factors involved (triggers and maintaining factors), remains challenging. It is however well established that 3 main elements, known as Coumel's triangle, underlie the onset of AF: a predisposing substrate, a trigger event and an imbalance in the activity of the autonomic nervous system.^{2,14}

Even though the QT interval reflects ventricular electrical activities,¹⁸ Mandyam *et al.*¹¹ and Nielsen *et al.*¹² demonstrated an association between both the prolongation and the shortening of QT intervals and the risk of developing AF, thus suggesting that QT modifications may reflect alterations in atrial refractory periods. Although there are several differences between atrial and ventricular cells, there are overlapping potassium channels in both chambers.¹³ In 1998 Satoh *et al.*¹⁹ administered potassium channel blockers in a canine model, inducing polymorphic tachyarrhythmias in the atrium as well as in the ventricle. In 2016 Nguyen *et al.*¹⁴ found a positive correlation between QTc and the atrial effective refractory period (AERP). It is therefore possible to infer that an abnormal QTc may reflect alterations in atrial refractoriness; patients with a prolonged QT-associated AF may have a longer AERP, which could determine a major susceptibility to atrial tachyarrhythmias. Moreover, patients with congenital long QT syndrome (LQTS) and short QT syndrome (SQTS) have alterations in atrial action potentials' duration and they are more susceptible to develop atrial tachyarrhythmias, such as AF.^{20,21}

To our knowledge, this is the first study comparing QTc and QT/QTc variability before AF onsets and non-triggering supraventricular ectopic beats in the same time frame and patient; in our opinion this potentially limits interpersonal variability and, especially, differences within each's patient conditions otherwise biasing the analysis. In our study, comparisons between AF triggers and

NTSVEBs revealed statistically significant differences in mean QTc and QT/QTc variability; therefore, a greater variation in ventricular repolarization could indirectly reflect alterations of atrial repolarization, which is a major determinant of AF onset, perhaps through the increase of the window of myocardial tissue vulnerability.

The autonomic nervous system (ANS) plays an important role in the onset of AF, likely also by exerting a major influence on QT variability by heart rate variation²². Although it was initially thought that increased vagal tone was responsible for every AF onset, in 2001 Zimmerman *et al.*²³ demonstrated fluctuations of the autonomic in favor of either vagal or adrenergic tone before AF onsets. For this reason, most recent literature, distinguished between vagal and adrenergic AF onsets according to the LF/HF ratio before the arrhythmia episodes, proving the presence of statistically different changes in the ANS activity before different types of AF episodes, that also present different intrinsic characteristics^{24 25}. By comparing QT intervals and their variability before vagal and adrenergic onsets, no significant difference, however, emerged in our study. Increased vagal tone may be a possible cause of prolonged QT and may increase its variability, although this also occurred before adrenergic triggers, with the high frequency HRV parameter, reflecting parasympathetic activity, increasing before the trigger.^{23,24} Calculating QTc interval for each episode, we believe the influence of heart rate alone limited.

A different classification of AF initiation patterns was suggested by Lu *et al.*,¹⁷ subdividing the onsets into type I and type II based on the CLV₃₀ higher or lesser than 10%. The comparison between type I and type II triggers and their respective NTSVEBs also did not report significant differences in our study. We can therefore deduce that the increase in the variability of repolarization has major importance no matter what the trigger type is.

LIMITATIONS:

Only AF episodes that were longer than 30 seconds were analyzed; therefore, no conclusion can be made for shorter episodes.

Due to the strict criteria required from the Task Force recommendations¹⁶ for a truthful HRV analysis, many AF episodes had to be excluded due to the presence of artefacts or major ectopic activity; while reducing the number of episodes analyzed, this endorsed high quality calculations and realistic, reproducible results.

The comparison between HRV and repolarization analyses is undermined by the different temporal windows required: while HRV analysis requires a 5 minutes period to be conducted, the QT analysis is performed in just a few seconds.

Moreover, 3-lead ECG Holters were employed, thus limiting QT calculations.

All the patients were under pharmacological treatment during Holter recordings and this could have altered the analysis' results. Although it is well known that AADs and beta-blockers exert effects on QTc duration and variability, unfortunately too few patients were enrolled in the present study to consider the role of these drugs.

Lastly, two different softwares have been used for the analysis. Algorithms and frequency ranges for HRV analysis were identical (0.04-0.15 Hz for LF and 0.15-0.40 Hz for HF); we cannot, however, exclude that unpredictable variations might exist.

CONCLUSION:

Prolongation and increasing variability of QT intervals on superficial ECG recording suggest an important electrical substrate, at least co-responsible for the genesis of AF, no matter what the trigger type is. This observation should lead to further studies and be used for the evaluation and monitoring of antiarrhythmic therapies.

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