Age, gender and drug therapy influences on Tpeak-tend interval and on electrical risk score

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ABSTRACT

Background and objectives: Electrical risk score (ERS) has been proposed as easy, inexpensive test to stratify of sudden cardiac death (SCD) risk in subjects with normal left ventricular function. Potentially, aging, gender and drugs can influence ERS affecting two on six electrical markers, particularly, those based on the repolarization. Aim of this study was to establish aging, gender and drug therapy possible influences on ERS and mortality in elderly patients.

Method: 237 consecutive, low SCD risk-outpatients with asymptomatic and treated cardiovascular risk factors were analyzed. Six simple ECG markers composed ERS: heart rate (>75 bpm); left ventricular hypertrophy (Sokolow-Lyon criteria); delayed QRS transition zone (≥V4), frontal QRS-T angle (>90°), long QT_{Bazett}; long T peak to T end interval (T_{p-e}). We obtained ERS in 237 outpatients, grouped according age (<40 ys, ≥40 to <60 ys and ≥60 ys), gender and drug therapy with or without possible influence on the repolarization phase.

Results: Two-hundred-thirty-seven patients were grouped respectively in the following age classes: <40 years old; ≥40 to <60 years old and ≥60 years old. ERS ($p < 0.05$), QT_{Bazett} ($p < 0.001$), T_{p-e} ($p < 0.001$) were higher in older subjects independently from gender, drug therapy and cardiovascular comorbidity. After two years we reported a 7.3% of mortality in the older groups; age (deceased versus survivors: 80 ± 4 versus 73 ± 7 years, $p < 0.05$) and T_{p-e} (deceased versus survivors: 117 ± 15 versus 93 ± 21 ms, $p < 0.05$) were significantly lower in survivors, multivariable logistic regression analysis selected only the T_{p-e} as significant risk factor for total mortality (odd ratio 1.06, 95% CI: 1.01–1.12, $p < 0.05$).

Conclusion: Aging was associated to the ERS and repolarization phase derangement. T_{p-e} should be considered a marker of total mortality rather than SCD in the over sixty years old patients.

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Introduction

The holy grail of modern cardiovascular medicine was to find a simple and inexpensive test capable to identify subjects, candidate to malignant arrhythmias in a population with low risk of sudden cardiac death (SCD). Recently, some authors proposed the electrical risk score (ERS) [1], this score, based on standard 12 lead ECG, should be able to detect subjects with reasonable risk of SCD. This ERS was composed by six different ECG data: heart rate, LVH, QRS transition zone, QRS-T angle, QT (QT_{Bazett}), and Tpeak to-Tend segment (T_{p-e}), then two on six are based on the left ventricular repolarization. Recently, two different studies reported that the increase this score it was related with high risk SCD in two different populations [1,2]. In fact, these authors

reported a high risk of SCD both in apparently healthy subjects with normal ejection fraction [1] and the subjects with degenerative aortic stenosis [2]. Because left ventricular repolarization duration (QT_{Bazett}, T_{p-e}) could be affected by aging, gender and drug administration and, it could play also a decisive rule in this score. Aim of this study was to evaluate the possible influence of these three different clinical parameters on repolarization data, the ERS and the mortality in old patients with low risk of SCD.

Methods and materials

Participants

A total of 237 consecutive outpatients received a standard 12-lead electrocardiogram between April and December 2016. All these patients had low risk of SCD, in fact they reported a asymptomatic history of

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treated vascular risk factors (hypertension, diabetes, hypercholesterolemia) or chronic heart failure with normal systolic function, with or without mild symptoms (I or II NYHA), stable or treated coronary diseases etc. We did not included patients with severe heart failure (III-IV NYHA class), dilated cardiomyopathy with low ejection fraction, aortic valve stenosis or hypertrophic cardiomyopathy or others known diseases with high risk of SCD or patients with implantable cardioverter defibrillator device (ICD) indication. All participants provided their written informed consent. We grouped the patients in base to the age, or drug therapy with possible effect on the repolarization or gender. According to age the groups were three: subjects aged <40 years, ≥40 to <60 years, ≥60 years. In the same manner, we grouped the patients according to the drug therapy: subjects without therapy with possible effect on the left ventricular repolarization phase; subjects with one drug with the possible effect on the left ventricular repolarization phase; and subjects with two or more drugs with possible effect on the ventricular repolarization phase. The drugs with possible effect on QT were obtained by web site: www.crediblemeds.org. In the our study population, we considered the following drugs to have not influence on repolarization phases: antiplatelet drugs; ACE inhibitors; sartans; β-blockers; statins; diltiazem or verapamil; dihydropyridine calcium channel blockers; α-adrenoreceptor-blockers; oral anticoagulants; aldosterone antagonists; digoxin; potassium; levothyroxine; methimazole; nitrates; ω-3-polynsatured fatty acid; ivabradine; insulin; oral antidiabetic drugs; β-2-adrenoreceptor-agonists; anticholinergic bronchodilatators; corticosteroids; pain reliefs; benzodiazepines; dopa-decarboxylase inhibitors; other antiparkinson drugs (selegiline, pramipexole); gabepentin; lamotrigine; eletriptam; vitamin D3; 5-α-Reductase inhibitors; lactulose; antivertigo drugs; allopurinol. On the contrary, we considered the following drugs to have a possible influence on repolarization phases: protonic pomp inhibitors, histamine-2-receptors blockers; furosemide; propafenone; flecainide; amiodarone; ranolazina; antidepressants: selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrin reuptake inhibitor (SNRI), noradrenergic and specific serotonergic antidepressant (NSSA) and triclycs; neuroleptics; acetylcholinesterase inhibitors; memantine; pregabalin; amantadine; carbamazepine; valproate; levetiracetam; antihistamines; macrolides or chinolones; tizanidine; domperidone; hidroxychloroquine.

Electrocardiographic analysis

Each enrolled patient had a stored resting 12-lead ECG (Esaote, model: MyCardioPad/XL 12 channels, Florence, Italy) available for the analysis (paper speed was 25 mm/s and calibration 10 mm/mV). Those patients with ECG evidence of atrial flutter or II/III-degree atrioventricular block, pre-excitation, or paced rhythm were excluded from analysis. Heart rate, LVH (Sokolow–Lyon criteria), delayed QRS transition zone, frontal QRS-T angle, long QT_{Bazett}, and long T_{p-e} composed the ERS [1,2]. In this score 1 and 0 were assigned respectively for an abnormal or normal ECG electrical value, and a score ≥4 was considered predictive of high risk for mortality [1,2]. Abnormal ECG data were considered as the following: a heart rate >75 bpm, QRS duration >110 ms, the left ventricular hypertrophy, achieved with the Sokolow–Lyon criteria, the QRS transition ≥4th precordial lead (V4), the frontal QRS-angle >90°, and T_{p-e} >89 ms [1,2]. Frontal QRS-T angle was calculated as the difference between T wave and QRS axis; in case the difference between QRS and T axis was higher than 180°, QRT-T angle was calculated by subtracting these achieved degrees from 360° [3]. Moreover, with regard to repolarization phase, we corrected the QT intervals by the Bazett method (QT_{Bazett}: $QT/RR^{0.5}$). Respectively, a QT_{Bazett} interval >450 ms for men and >460 ms for women. Tpeak-tend was manually evaluated with tangent method using an electronic caliper and also with an online program uploading scanned copies. The same skilled cardiologist (GP) analyzed all ECGs in order to eliminate inter-observer bias.

The patients provided informed consent for the use of their data for research purpose and the study was in accordance with good clinical practice and the principles of the Declaration of Helsinki of clinical research involving human patients. Local Ethical Committee approved this study.

Statistical analysis

Normally distributed continuous variables are reported as mean and standard deviation and are compared using one-way analysis of variance and Bonferroni test. Non-normally distributed variables are expressed as median and inter-quartile range [IQR] and compared using the Kruskal-Wallis and Mann–Whitney *U* tests. ERS' cut off was obtained from the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study [1]. Categorical variables are presented as frequencies and percentage and compared using the chi-squared test. Uni- and multivariable forward (A. Wald) stepwise logistic regression analysis were used to determine the association between all-cause mortality in the elders and the other selected clinical, or electrical covariates included in the study. Included covariates were: age, gender, heart rate, QRS, QTc, T_{p-e}, QRS-T angle, QRS transition zone, transition zone, left ventricular hypertrophy (Sokolow–Lyon criteria) and ERS.

Results

Two-hundred-thirty-seven patients underwent a standard electrocardiogram; 72, 50 and 115 subjects were grouped respectively in the following age classes: <40 years old (young subjects); ≥40 to <60 years old (middle age subjects) and ≥60 years old (elders) (Table 1). BMI, systolic and diastolic blood pressure were significantly lower in the younger group ($p < 0.0001$), on the contrary the older groups reported the major comorbidities and drug treatments for these comorbidities (Table 1). The drug therapy was different in three age-groups. Especially in the elders, we reported a significant difference regarding to the cardiovascular drugs (antiplatelet, sartans, ACE inhibitors, dihydropyridine calcium channels blockers, oral anticoagulants, furosemide), pomp protonic inhibitions, α-adrenoreceptor-blockers and 5-α-reductase inhibitors administration (Table 1) in comparison other the young and middle age subjects. We did not observed other statistic difference for other single drug administration between the groups. In conclusion, when we consider the overall burden of drugs with possible effect on repolarization the number of elders with 1 or 2 or more drugs with possible effect on repolarization were significantly higher than meddle age and younger patients ($p < 0.001$) (Table 1). Obviously, the young subjects without therapy with possible effects on repolarization were higher significantly in comparison to the other two groups ($p < 0.001$) (Table 1).

Elders showed a significantly higher of ERS ($p < 0.001$), QT_{Bazett} ($p < 0.05$) and T_{p-e} ($p < 0.001$) than young and middle age subjects (Table 2); on the contrary, young group reported an increase of the LVH ($p < 0.05$) and the frontal QRS-T angle ($p < 0.001$) in comparison to the middle age and elders (Table 2). Subjects without any drug therapy with possible influence on QT were younger than others subjects (Table 3) and these patients showed ERS ($p < 0.05$), T_{p-e} ($p < 0.001$), QRS-T angle ($p < 0.001$) significantly different from subjects with one or two or more drugs with possible effects on QT. QT_{Bazett} was shorter also in subjects without ($p < 0.001$) or one drug ($p < 0.05$) with repolarization possible effect in comparison to patients with 2 or more drugs (Table 3).

When we considered the ERS and the other electrical markers in elderly group, we observed only one significant difference: the subjects with two drugs with possible effect on QT had a significant longer QT_{Bazett} (442 ± 31 ms, $p < 0.05$) than the subjects of the same age group without drug administration with QT effects (415 ± 30 ms). In fact, for example, T_{p-e} was similar in elderly patients with different drugs administration (no drug: 91 ± 15 ms; 1 drug: 91 ± 20 ms; 2 or more drugs: 98 ± 23; p:ns).

Table 1
General characteristic of the study subjects.

	Age < 40 years N:72	Age ≥ 40 < 60 years N:50	Age ≥ 60 years N:115	p
Age, years	26 ± 8**┼┼	50 ± 6**	74 ± 7	<0.0001
M/F, n	32/40	21/29	53/62	ns
BMI, kg/m²	23 ± 5*┼	26 ± 5	25 ± 4	<0.0001
SBP, mm Hg	112 ± 12*┼	121 ± 15**	137 ± 21	<0.0001
DBP, mm Hg	72 ± 10**┼┼	80 ± 11	78 ± 9	<0.0001
Heart rate, b/m	67 ± 10	67 ± 11	64 ± 9	ns
Hypertension, n (%)	4(6)**	8(16)**	71(62)	<0.0001
Hypercholesterolemia, n (%)	2(3)*	3(6)	22(19)	0.0044
Diabetes, n (%)	1(1)*	1(2)*	15(13)	0.0066
Myocardial ischemia, n (%)	0(0)*	1(2)	10(9)	0.0200
Chronic heart failure (I or II NYHA), n (%)	0(0)*	0(0)*	15(13)	0.0006
Atrial fibrillation, n (%)	2(3)	0(0)*	11(10)	0.0323
Depression, n (%)	0(0)*	2(4)	13(11)	0.0111
Cognitive impairment, n (%)	0(0)*	0(0)	7(6)	0.0272
Migraine, n (%)	0(0)	2(4)*	0(0)	0.0266
Prostatic hypertrophy, n (%)	0(0)*	2(4)	15(13)	0.0047
Antiplatelet drug	2(3)**	4(8)**	59(51)	<0.0001
Furosemide, n (%)	0(0)**	4(8)	20(17)	0.0018
ACE/Sartans	1(1)**	8(16)*	60(52)	<0.0001
β-blockers, n (%)	2(3)**	2(4)*	28(24)	<0.0001
Statins, n (%)	2(3)**	4(8)*	33(29)	0.0001
Dihydropyridine calcium channel blockers, n (%)	1(1)*	0(0)*	18(17)	0.0005
α-adrenoreceptor-blockers, n (%)	0(0)*	0(0)*	17(15)	0.0062
Oral anticoagulants, n (%)	0(0)*	0(0)*	13(10)	0.0015
Protonic pomp inihibithors, n (%)	5(7)**	7(14)**	52(45)	<0.0001
No drug with possible QT influence, n (%)	61(85)**	36(62)**	39(34)	0.0007
1 drug with possible QT influence, n (%)	6(8)*	8(16)	39(34)	0.0028
2 or more drugs with possible QT influence, n (%)	5(7)*	6(12)*	37(32)	0.0017
No drug with possible QT influence, n (%)	61(85)**	36(62)**	39(34)	0.0007

Data are expressed as mean ± SD or number of patients (%); **$p < 0.001$ or *$p < 0.05$ patients with age < 40 years or age ≥ 40 < 60 years versus patients with age ≥ 60 years; ┼┼ $p < 0.001$ or ┼ $p < 0.05$ patients with age < 40 years versus patients with age ≥ 40 < 60 years.

At the end, we compare the ERS and other electrical markers between three age groups excluding the subjects with drug therapy with possible influence on QT, to assess the influence of aging on repolarization and ERS (Table 4). T_{p-e} ($p < 0.001$) and ERS ($p < 0.05$) was higher in elders (Table 4) in comparison to the other two groups; QT_{Bazett} was longer only in older than young subjects ($p < 0.05$) (Table 4).

Considering the whole study population, we did not find any difference between the two genders (M/F:105/131), for age (54 ± 23 vs 54 ± 22 years, p:ns), heart rate (67 ± 11 vs 68 ± 11 b/m, p:ns), T_{p-e} (82 ± 18 vs 84 ± 20 ms, p:ns), QRS-T angle (−9[50] vs −3[39] degree, p:ns) and ERS (1 [1] vs 1 [1], p:ns) On the contrary, QT_{Bazett} was significantly higher in the woman (411 ± 35 vs 420 ± 29 ms, $p < 0.05$) and LVH (2.66 ± 0.79 vs 2.38 ± 0.84 mV, $p < 0.05$) was higher in the males. The single age groups did not report any other statistic gender related differences except for the QT_{Bazett} in the woman young group (394 ± 23 vs 409 ms, $p < 0.05$).

We found some unexpected data, when we compared elders with cardiovascular diseases (hypertension, chronic heart failure, ischemic cardiomyopathy and atrial fibrillation) versus the same age-group, but without cardiovascular diseases, we did not observe any difference in ERS and in each single electrical marker.

After at least 2 years (mean 2.3 ± 0.5) we recall all 115 elders and we were able to get in touch 68 (M/F: 28/40), that it was 59% of original study population. In this period 5 (7.3%) elders died (M/F: 3/2), one for SCD and four for cognitive decline, immobility syndrome and related infective complications. All deceased patients of this group had a daily intake of 2 or more drugs with possible effect on repolarization. Between the deceased and survival elders we find only two significant differences: age (deceased versus survivors: 80 ± 4 versus 73 ± 7 years, $p < 0.05$) and T_{p-e} (deceased versus survivors: 117 ± 15 versus 93 ± 21 ms, $p < 0.05$). Univariable and multivariable logistic regression analysis selected only the T_{p-e} as significant risk factor for mortality (odd ratio 1.06, 95% CI: 1.01–1.12, $p < 0.05$).

Table 2
Electrocardiographic measures in patient groups with different age.

	Age < 40 years N:72	Age ≥ 40 < 60 years N:50	Age ≥ 60 years N:115	p
Heart rate, b/m	69 ± 10	69 ± 12	66 ± 11	ns
QT_{Bazett}, ms	403 ± 23**	411 ± 30*	426 ± 34	<0.0001
T_{p-e}, ms	76 ± 12**	71 ± 13**	93 ± 20	<0.0001
QRS-T angle, degree	14[30]**┼┼	−4[28]*	−22[58]	<0.0001
QRS transition zone,	2.79 ± 0.88	2.86 ± 0.98	2.71 ± 1.38	ns
Electrocardiographic left ventricular hypertrophy, mV	2.86 ± 0.83**┼	2.30 ± 0.59	2.38 ± 0.85	<0.0001
Electrical risk score	0.60[1]**	0.46[1]**	1.11[1]	<0.0001
Subjects with Electrical risk score = 0	39(54)	31(62)	33(29)	0.017
Subjects with Electrical risk score ≥ 4	0 (0)	0(0)	4(3)	ns

Data are expressed as mean ± SD, or number of patients (%), or median [interquartile range]; **$p < 0.001$ or *$p < 0.05$ patients with age < 40 years or age ≥ 40 < 60 years versus patients with age ≥ 60 years; ┼┼ $p < 0.001$ or ┼ $p < 0.05$ patients with age < 40 years versus patients with age ≥ 40 < 60 years.

Table 3

Drug therapy and electrocardiographic measures.

	No drug with possible QT influence	1 drug with possible QT influence	2 or more drugs with possible QT influence	p
	N:135	N:52	N:50	
Age, years	44 ± 21**╫	66 ± 15	69 ± 18	<0.0001
Heart rate, b/m	68 ± 11	66 ± 12	69 ± 11	Ns
QT$_{Bazett}$, ms	408 ± 26**	416 ± 35*	436 ± 34	<0.0001
T$_{p-e}$, ms	78 ± 15**╪	86 ± 22	93 ± 87	<0.0001
QRS-T angle, degree	4[39]**╫	−20[49]	−18[51]	<0.0001
QRS transition zone,	2.79 ± 0.98	2.68 ± 1.37	2.79 ± 1.38	Ns
Electrocardiographicleft ventricular hypertrophy, mV	2.62 ± 0.83	2.36 ± 0.82	2.35 ± 0.88	Ns
Electrical risk score	0[1]*╪	1[1]	1[2]	0.005
Subjects with Electrical risk score = 0	71(53)	17(33)	15(30)	ns
Subjects with Electrical risk score ≥ 4	1(1)	1(2)	2(4)	ns

Data are expressed as mean $\pm$ SD, or number of patients (%), or median [interquartile range]; ** $p < 0.001$ or * $p < 0.05$ patients without drug or one drug versus patients with two or more drugs with possible effect on repolarization; ╫ $p < 0.001$ or ╪ $p < 0.05$ patients without drug versus patients with one drug with possible effect on repolarization.

Discussion

The main important data of these study were: first of all, in over sixty year old patients with (Table 2) or without (Table 4) drug therapy with possible repolarization influence, we reported an increase of QT$_{Bazett}$, T$_{p-e}$ and the ERS; secondly, because the QT$_{Bazett}$, T$_{p-e}$ and the ERS were higher in tall older patients, but especially in the older subjects without drug therapy with possible repolarization interference (Table 4), aging should be considered an independent factor capable to influence these three parameters; thirdly, gender and heart disease had not influence on these parameters in elderly patients. Finally, the abnormal T$_{p-e}$ was the only parameter associated with a higher risk of mortality in over sixty-year-old patients and after short term follow-up.

As we previously pointed out, in our study, the repolarization was longer in over sixty-year-old independently from gender and drug therapy; regarding the gender, however, this datum was not novel, in fact a relation between age and QT has already been described [4]. In fact, in woman of child-bearing age, the estrogen or the testosterone absence [5] induces a longer QT (about 10 milliseconds) than the male subjects and, of course, after the menopause the repolarization duration is similar in both the genders. On the contrary, we did not find any gender related difference regarding T$_{p-e}$, but we observed an age-related increase of this parameter in previous studies, using other methods, confirming the weakness of this part of repolarization phase in the elderly patients [6]. All these observations induced us to assume, reasonably, that it exists in old patients a repolarization related risk of SCD, even if we have not studied a statistically significant number of subjects; anyway, T$_{p-e}$ was associated in total mortality risk in elderly subjects.

The supposable age-related mechanisms, capable to affect repolarization, could be numerous, but understudied. Obviously, the prolongation of this phase could involve an imbalance of the ion channel current control; for example, it was reported an abnormal cardiomyocyte calcium handling. In particular, L-type calcium channel current showed a slower inactivation and, similarly, these channels show increased activity and number [7]. Moreover, it could be also involved a reduction in outwardly directed potassium currents: in fact, it was recently reported an age-dependent remodeling of slow and rapid outward rectifying currents in experimental model. [8].

In conclusion, in this study we observed an increase of repolarization duration phase and ERS in older patients. ERS was not a predictor of SCD in these patients after two years, but the small size of examined sample and the short period of follow-up could be the causes of these inconclusive results. On the contrary, T$_{p-e}$, a simple and inexpensive parameter based on the standard ECG, was an independent risk factor of mortality in these old patients. Gender, cardiac diseases and drugs with possible effect on repolarization did not influence the ERS, the repolarization and the outcome in patients over sixty without advanced heart failure.

Disclosure/Acknowledgments

Authors have not any conflict of interest in this paper to declare.

CRediT authorship contribution statement

Gianfranco Piccirillo: Conceptualization, Data curation, Formal analysis.**Federica Moscucci:**Writing - review & editing.**Marcella Fabietti:**Investigation, Methodology, Data curation.**Claudia Di Iorio:**Investigation, Methodology, Data curation.**Fabiola Mastropietri:**Investigation, Methodology, Data curation.**Teresa Sabatino:**Investigation, Methodology, Data curation.**Davide Crapanzano:**Investigation, Methodology, Data curation.**Gaetano Bertani:**Investigation, Methodology, Data curation.**Giulia Zaccagnini:**Investigation, Methodology, Data curation.**Ilaria Lospinuso:**Investigation, Methodology, Data curation. **Damiano Magrì:**Supervision, Validation, Visualization, Writing - review & editing.

Table 4

Electrocardiographic measures in patient groups with different age without drug therapy with possible influence on QT.

	Age < 40 years	Age ≥ 40 < 60 years	Age ≥ 60 years	p
	N:61	N:36	N:38	
Heart rate, b/m	68 ± 10	70 ± 10	66 ± 13	ns
QT$_{Bazett}$, ms	401 ± 23*	414 ± 26	415 ± 30	0.009
T$_{p-e}$, ms	75 ± 12**	70 ± 13**	91 ± 15	<0.0001
QRS-T angle, degree	14[29]	0[37]	−14[57]	ns
QRS transition zone,	3 ± 1	3 ± 1	3 ± 1	ns
Electrocardiographic left ventricular hypertrophy, mV	2.75[0.64]*	2.35[0.80]	2.23[1.03]	0.016
Electrical risk score	0[1]*	0[1]*	1[2]	0.04
Subjects with Electrical risk score = 0	35(57)	21(58)	15(39)	ns
Subjects with Electrical risk score ≥ 4	0(0)	(0)	1(3)	ns

Data are expressed as mean $\pm$ SD, or number of patients (%), or median [interquartile range]; ** $p < 0.001$ or * $p < 0.05$ patients with age < 40 years or age ≥ 40 < 60 years versus patients with age ≥ 60 years.

Declaration of competing interest

All authors deny conflicts of interest in connection with the submitted article, nor industry relationship.

References

[1] Aro AL, Reinier K, Rusinaru C, Uy-Evanado A, Darouian N, Phan D, et al. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. Eur Heart J 2017;38(40):3017–25 Oct 21.

[2] Piccirillo G, Moscucci F, Mastropietri F, Di Iorio C, Mariani MV, Fabietti M, et al. Possible predictive role of electrical risk score on transcatheter aortic valve replacement outcomes in older patients: preliminary data. Clin Interv Aging 2018;13:1657–67 Sep 11.

[3] Chua KC, Teodorescu C, Reinier K, Uy-Evanado A, Aro AL, Nair SG, et al. Wide QRS-T angle on the 12-lead ECG as a predictor of sudden death beyond the LV ejection fraction. J Cardiovasc Electrophysiol 2016;27(7):833–9 Jul.

[4] Rabkin SW, Cheng XJ, Thompson DJ. Detailed analysis of the impact of age on the QT interval. J Geriatr Cardiol 2016;13(9):740–8 Sep.

[5] Piccirillo G, Moscucci F, Pofi R, D'Alessandro G, Minnetti M, Isidori AM, et al. Changes in left ventricular repolarization after short-term testosterone replacement therapy in hypogonadal males. J Endocrinol Invest 2019;42(9):1051–65.

[6] Piccirillo G, Moscucci F, Pascucci M, Pappadà MA, D'Alessandro G, Rossi P, et al. Influence of aging and chronic heart failure on temporal dispersion of myocardial repolarization. Clin Interv Aging 2013;8:293–300.

[7] Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin 2012;8(1):143–64 Jan.

[8] Ocorr K, Zambon A, Nudell Y, Pineda S, Diop S, Tang M, et al. Age-dependent electrical and morphological remodeling of the Drosophila heart caused by hERG/seizure mutations. PLoS Genet 2017;13(5):e1006786.