XXVI Congresso Brasileiro de Engenharia Biomédica

Armação de Búzios – RJ – Brasil

October 21st to 25th, 2018

Ventricular repolarization to RR-interval adaptation delay is a marker of sudden cardiac death in subjects with Chagas' heart disease

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Background, Motivation and Objective. In physiological conditions, cardiac action potential adapts to inter-beat interval fluctuations concordantly, making it possible mechanical and electrical events of the heart to fit cardiac cycle length. On the surface ECG, this phenomenon corresponds to the adaptation of the ventricular repolarization duration (VRD) to preceding RR-interval variations. However, in the presence of heart disease, the adjustment of VRD to RR-interval (VRD-RR coupling) may be delayed, taking additional beats to adapt. Delayed repolarization adaptation (DRA) may cause repolarization duration to remain unchanged in subsequent heartbeats after RR-interval shortening, potentially making it vulnerable to R/T phenomenon and life-threatening arrhythmia. This study investigated VRD-RR coupling in healthy subjects and in patients with chronic Chagas cardiomyopathy (CCC) who experienced sudden cardiac death aiming at assessing the clinical value of DRA in this setting.

Methods. In a prospective observational study, age, gender and left ventricular systolic function adjusted, 20 subjects with CCC (nine sudden cardiac death and 11 survivors) and 20 consecutive healthy subjects (Normal) were included ([mean ± SD] 52.5 ± 13.1 years old, 10 males and 10 females). All subjects were in sinus rhythm and had *XYZ* modified *Frank* leads high resolution ECG acquired in supine position during 20 min, after 10 min of rest. The cross-correlation function between VRD (defined as QT-interval) and RR-interval was quantified until sixth subsequent beat. Starting from a reference heartbeat, DRA was defined as the number of beats after the reference one with the highest significant correlation coefficient (max RR vs QT correlation). Left ventricular systolic function was assessed by left ventricular ejection fraction (LVEF) on 2D echocardiogram. Selected patients in CCC group underwent cardiac magnetic resonance imaging (CMRI) with gadolinium contrast to assess the amount of ventricular fibrosis (in gram). Additionally, the following variables were assessed on ECG: mean and SD of RR-intervals, uncorrected and corrected QT-interval (QTc [Friderica]) and TpTe intervals. CCC subjects were clinically stable and were regularly followed-up in outpatient clinics. SCD was ascertained by review of medical records and death certificates. Variables are expressed as mean ± SD. Kruskal-Wallis One-way ANOVA and Student 't' tests compared groups where appropriate. Correlation was assessed by Pearson`s test. ROC curve analyses were assessed to identify optimal cut-off values and respective diagnostic yield. A multivariate Cox-regression model assessed independent predictors of SCD. Alpha error level was 0.05.

Results. The mean overall follow up for CCC was 12.9 ± 3.2 year (258 patients.year), and those who experienced SCD was 10.8 ± 3.2 years. Table 1 summarizes the results. For Normal, CCC survivors and CCC SCD, the average max RR vs QT correlation was, respectively, 0.62, 0.57 and 0.68 ($p < 0.05$ for all). The only variables significantly related to SCD among CCC were: mean RR-interval (Normal - 1018 ± 155 ms; CCC survivors - 1059 ± 137 ms; CCC SCD - 891 ± 105 ms; $p < 0.05$), mean TpTe interval (Normal – 84.1 ± 16.7 ms; CCC survivors – 85.2 ± 20.9 ms; CCC with SCD -

72.3 ± 59.2 ms; $p < 0.05$) and DRA (Normal - 0.8 ± 1.4 beats; CCC survivors - 0.2 ± 0.4 beats; CCC with SCD - 2.2 ± 2.5 beats; $p < 0.05$). Between CCC survivors and CCC SCD, ROC curve analysis for mean RR-interval, TpTe interval and DRA yielded, respectively, AUC 0.83 ± 0.09 ($p < 0.05$; optimal cutoff value ≤ 864 ms; 100% specificity, 56% sensitivity), AUC 0.79 ± 0.12 ($p < 0.05$; optimal cutoff value ≤ 78 ms; 82% specificity, 78% sensitivity) and AUC 0.74 ± 0.11 ($p < 0.05$; optimal cutoff value ≥ 2 beats; 100% specificity, 56% sensitivity). In a stepwise multivariate regression model, mean RR-interval (beta = 1.7; $p < 0.05$) and DRA (beta = 1.9; $p < 0.05$) were independent predictors of SCD (pseudo $r^2 = 0.72$; model $\chi^2_2 = 12.4$; $p < 0.05$). DRA correlated significantly with myocardial fibrosis on CMRI ($r = 0.55$; $p < 0.05$).

Discussion and Conclusions. In healthy subjects, VRD tends to adapt instantaneously to RR-interval variations. In CCC who experienced SCD, on the other hand, VRD presents a delayed adaptation to RR-interval fluctuation, either lengthening or shortening, when compared to both CCC survivors and healthy subjects. Both mean RR-interval and DRA are independent predictors of SCD in CCC population. Particularly, DRA is correlated with amount of myocardial fibrosis, indicating subjacent myocardial damage. Delayed repolarization adaptation represents a potential marker for sudden cardiac death in chronic Chagas cardiomyopathy population.

Table 1. Comparison of demographic, echocardiographic, cardiac MRI and ventricular repolarization parameters

Variable	Normal	CCC survivors	CCC SCD	*p*
Age (years old)	51.4 ± 16.5	52.7 ± 7.0	54.4 ± 11.1	NS*
LVEF (%)	72 ± 6	65 ± 8	58 ± 13	NS*
CMRI fibrosis (g)	-	4.5 ± 5.6	10 ± 8.9	NS**
Mean RR-interval (ms)	1018 ± 155	1059 ± 137	891 ± 105	< 0.05*
Mean QT interval (ms)	399.7 ± 31.3	420.6 ± 69.2	384.8 ± 45.3	NS*
SD QT interval (ms)	2.2 ± 0.8	4.7 ± 4.0	5.8 ± 2.2	NS*
Mean QTc interval (ms)	393.5 ± 21.8	407.1 ± 57.1	403.4 ± 30.4	NS*
SD QTc interval (ms)	5.8 ± 2.6	5.4 ± 2.1	6.9 ± 5.6	NS*
Mean TpTe interval (ms)	84.1 ± 16.7	85.2 ± 20.9	72.3 ± 59.2	< 0.05*
SD TpTe interval (ms)	2.7 ± 1.2	5.1 ± 3.4	7.4 ± 3.3	NS*
Max RR vs QT correlation	0.62 ± 0.13	0.57 ± 0.21	0.68 ± 0.15	NS*
Delayed repolarization adaptation (beat)	0.8 ± 1.4	0.2 ± 0.4	2.2 ± 2.5	< 0.05*

* Kruskal-Wallis ANOVA test; ** Student 't' test; LVEF – left ventricular ejection fraction; CMRI – cardiac magnetic resonance imaging; SD – series standard deviation

Acknowledgment. This study received financial support from the Brazilian agencies CNPq and FINEP.

Keywords. Chagas heart disease; ventricular repolarization duration; RR-interval; delayed repolarization adaptation; left ventricular systolic function; myocardia fibrosis