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Research Article

Beat-To-Beat Ventricular Repolarization Duration Variability Assessed By Cardiac Acceleration and Deceleration Phases in Athletes

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Abstract

Dynamic ventricular repolarization duration (VRD) and *RR-interval* coupling relates to autonomic control and myocardial electrical stability. Phase-rectification of *RR-interval* series separates acceleration (AC) and deceleration (DC) phases, reflecting sympathetic and parasympathetic influences on heart rate, respectively. To assess the effect of physical conditioning status on dynamic VRD and phase-rectification-driven RR-interval coupling. Controls (n = 10) and Athletes (n = 10) groups underwent 15 min resting ECG. *RR-interval* histogram was calculated, with 100 ms width classes, ranging from 700 ms to 1300 ms. *RR-intervals* and respective VRD, defined as the segment between R-wave peak and the apex of the T-wave (RT^A) were grouped. The averages of RT^A (MRT^A) and *RR-intervals* (MRR) were calculated, using the whole series, AC and DC phases, as well as root-mean-squared difference of consecutive RT^A ($RMS\text{-}RT^A$). Values were pooled, and compared inter groups and inter classes. Regression lines were calculated, and slope compared between groups ($\alpha<0.05$). MRT^A was larger in Athletes than in Controls. MRT^A increased proportionally to MRR in both AC and DC, and slope was steeper in Athletes. MRT^A slopes in AC and DC phases did show differences, in both groups. $RMS\text{-}RT^A_{AC}$ and $RMS\text{-}RT^A_{DC}$ showed no intergroup differences. An inverse correlation between $RMS\text{-}RT^A$ and MRR was found only in Athletes, similarly in both phases. In athletes, VRD is larger, for all *RR-interval* durations, and RT^A slope steeper than in heathy sedentary, indicating faster adaptation. In athletes, VRD variability decreases as *RR-interval* increases, indicating a beneficial effect of fitness on repolarization stability.

Keywords: *Ventricular repolarization duration; Cardiac cycle length; RR-interval histogram; Heart rate adaptation; Phase rectified RR-interval*

Abbreviations: ECG: electrocardiogram; VRD: ventricular repolarization duration; AC: acceleration; DC: deceleration; RR: interval segment duration between consecutive R-wave peaks; RT^A: segment between R-wave peak and the apex of the T-wave; MRT^A: averages of RT^A; MRR: averages of *RR-intervals*; RMS: root-mean-squared; HR: heart rates; ECG: electrocardiogram; VO_{2MAX}: maximal oxygen consumption; METs: metabolic equivalents; SD: standard deviation; HRV: heart rate variability; PRSA: phase-rectified signal averaging

Introduction

Regular exercise leads to structural and functional adaptations that improve cardiac function as a consequence of increased demand on the cardiovascular system [1,2]. Among them, are i) increases in left ventricular mass and volume [3], ii) reduced resting heart rates (HR) induced by increased vagal tone [4,5] and, iii) electrical changes, characterized by the redistribution of electrical charges on myocardial surface, as indicated by increases in both ventricular activation amplitude and repolarization duration (*QT-interval*), which are observed in the resting electrocardiogram (ECG) waveforms of athletes [6,7].

The relationship between ventricular repolarization duration (VRD) and cardiac cycle length is a valuable tool to assess cardiac adaptation to autonomic input [8]. It is well known the VRD adapts to changes in HR, which makes it difficult to compare the repolarization interval for subjects with different physiological conditions. The effects of exercise training on VRD indices may have an autonomic nature, partially explained by an increase in cardiac vagal activity [9] and, additionally, have not been extensively studied.

Recently, an approximate isolation of distinct autonomic contribution on HR has been possible by assessing the capability of *RR-interval* series to accelerate (AC) and decelerate (DC), representing, respectively, sympathetic and parasympathetic contribution phases. To further accomplish this task, it is initially detected whether a particular *RR-interval* increases or decreases relatively to the previous one, and then such particular *RR-intervals* are separated in new series [10].

Previous studies reproduced the VRD dependence on the cardiac cycle lengths, indicating that the separation by *RR-interval* classes can be useful to compare different populations based on pairing the bands [11]. Additionally, depending on vagal stimulus intensity, the ascending rate of the *RR-interval* series (DC phase) changes accordingly, determining steepest slope variation [12]. Then, discriminating the DC and AC series, a strongest vagal stimulus would determine faster ventricular adaptations (steepest curve) and vice-versa, potentially affecting the relation between them (hysteresis). Thus, the objective of the study was: i) to develop an analysis that relates the ventricular repolarization duration and its variability to *RR-intervals*, stratified by RR histogram classes, comparing healthy sedentary subjects and athletes, and ii) to assess AC and DC phases of *RR-interval* series, discriminating sympathetic and parasympathetic effects.

Materials and Methods

Study population

The analyzed signals were extracted from an existing high resolution ECG database as described previously [5]. The study protocol was approved by Instituto Nacional de Cardiologia Ethics Committee and informed consent was obtained from each volunteer. Ten elite runners ([mean ± SD] 8.9 ± 3.2 years of training; six to eight training sessions/week; 90 to 120 min/session; 90 to 110 km/week) were enrolled (Athlete group). A group of 10 healthy sedentary volunteers were included as control (Control group). Inclusion criteria, physical assessment procedures and maximal oxygen consumption (VO_{2MAX}) estimation protocol have been published elsewhere [5].

VO_{2MAX} was divided by the constant 3.5 mL kg^{-1} min^{-1} to be converted into metabolic equivalents (METs). Control and Athlete groups were separated according to estimated VO_{2MAX}, by arbitrarily defining as less than 11.5 METs for sedentary controls and more than 16.0 METs for athletes.

Both groups were adjusted by age, gender and matched by anthropometric data (Table 1). The aim of anthropometric data intergroup matching was to minimize inter-group physiological and anthropometric variability, thus reducing potential effect of thoracic geometry on surface ECG signals.

	Controls	Athletes
Age (years)	29.0 ± 5.4	24.4 ± 7.2
BMI (Kg/m^2)	23.8 ± 3.8	20.7 ± 1.9
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2
APTD (cm)	21.3 ± 1.9	21.1 ± 1.2
LLTD (cm)	28.1 ± 3.2	28.0 ± 1.2
METs	8.7 ± 1.9	19.6 ± 1.3*

Table 1: *Anthropometric and demographic characteristics (mean ± SD) of the subjects who participated in the study. BMI: body mass index; BSA: body surface area; APTD: anteroposterior thoracic diameter; LLTD: laterolateral thoracic diameter; METs: metabolic equivalents *p = 0.001.*

Signal acquisition and processing

The high resolution ECG signals were acquired using modified bipolar Frank XYZ orthogonal leads shortly after application of the questionnaire and physical examination. Before a 15 min continuous signal acquisition, subjects remained in the supine position for 5 min for stabilization of autonomic modulation after the change from the orthostatic position. Detailed description of the equipment was previously described and digital data were processed with custom-made pattern recognition software [13].

Wave detection

The analysis of the *RR-interval* length was carried out after detection of the *QRS* complex. Arti-facts and ectopic beats were excluded by correlation, precocity and visual inspection, by one expert.

The analysis of the VRD was carried out with the signal low-pass filtered at 15 Hz (Butter-worth, 2nd order). The distance between the top of the *QRS* complex *(R*) and the apex of the *T* wave (T^A) in normal beats defined RT^A interval, which was employed in a sole purpose of analyzing repolarization adaptation over instantaneous cardiac cycle [11]. The R point was defined as the absolute maximum of the *R*-wave, as well as the apex of the *T*-wave (T^A, Figure 1). The *RR*- and RT^A-intervals were analyzed on *X* lead.

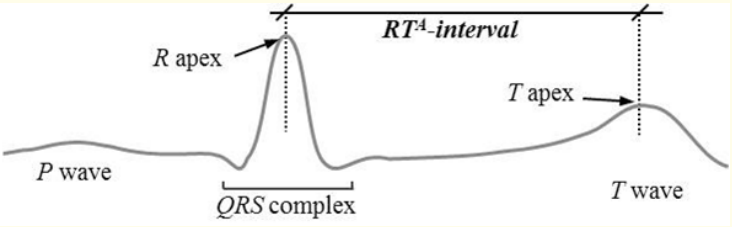

Figure 1: *Identification of the apex (point) on R- and T-waves, which allowed precise identification of the ventricular repolarization duration by RTA interval.*

Instantaneous RR and RTA interval analysis

The histogram was constructed for each individual *RR-interval* series, and divided into classes of 100 ms width, ranging from 700 ms to 1300 ms, which represents a variation between 46 and 100 bpm in HR. For each histogram class, and respective to each *RR-interval* series, it was calculated mean (*MRR*), standard deviation (*SDRR*) of consecutive normal *RR-intervals*, and mean (MRT^A), standard deviation ($SDRT^A$) and root-mean-squared difference ($RMS\text{-}RT^A$) of consecutive normal RT^A intervals. Only pairs of consecutive normal *RR* and RT^A intervals for individual series that lied inside a particular class of the *RR* histogram were analyzed together.

For a particular histogram class (class) of the i^{th} series, containing $N_{i,\,class}$ *RR-intervals*, the calculus of the mean ($Mx_{i,\,class}$), standard deviation ($SDx_{i,\,class}$), root-mean-squared difference ($RMSx_{i,\,class}$) of the normal RR and RT^A intervals was performed as follows:

$$Mx_{i,class} = \sum_{k=1}^{N_{i,class}} \frac{x_K}{N_{i,class}} \quad (1)$$

$$SDx_{i,class} = \sqrt{\sum_{k=1}^{N_{i,class}} \frac{(x_K - Mx_{i,class})^2}{N_{i,class}^{-1}}} \quad (2)$$

$$RMSx_{i,class} = \sqrt{\sum_{k=1}^{N_{i,class}} \frac{(x_k - x_{k-1})^2}{N_{i,class}}} \quad (3)$$

where x represents either *RR* or RT^A interval.

For each histogram, classes with 20 or less intervals were excluded of analysis to avoid bias due to lack of statistical precision.

The values of the variables $Mx_{i,\,class}$, $SDx_{i,\,class}$ and $RMSx_{i,\,class}$ were aggregated to the respective histogram class. The pooled mean ($Mx_{\,class}$), standard deviation ($SDx_{\,class}$) and root-mean-squared difference ($RMSx_{class}$) of RR and RTA intervals for each histogram class, weighted by respective degree-of-freedom ($\eta_{i,\,class}$), were calculated according to:

$$Mx_{class} = \frac{\sum_{i=1}^{20} Mx_{i,class} \cdot (\eta_{i,class} + 1)}{\sum_{i=1}^{20} (\eta_{i,class} + 1)} \quad (4)$$

$$SDx_{class} = \sqrt{\frac{\sum_{i=1}^{20} (SDx_{i,class})^2 \cdot \eta_{i,class}}{\sum_{i=1}^{20} \eta_{i,class}}} \quad (5)$$

$$RMSx_{class} = \sqrt{\frac{\sum_{i=1}^{20} (RMSx_{i,class})^2 \cdot (\eta_{i,class} + 1)}{\sum_{i=1}^{20} (\eta_{i,class} + 1)}} \quad (6)$$

where x represents either *RR* or RT^A interval.

The variables $MRT^A_{\,class}$ and $RMS\text{-}RT^A_{\,class}$ were plotted and correlated with $MRR_{\,class}$.

Instantaneous AC and DC analysis

RR-interval histograms in AC and in DC phases were also built, following the rules described above. *RR-interval* in AC ($RR_{\,AC}$) and in DC ($RR_{\,DC}$) phases was classified accordingly. To further accomplish this task, it was initially isolated the data points as either acceleration (AC) or deceleration (DC) phases. If a particular *RR-interval* increased relatively to the previous one, a DC interval occurred. As the instantaneous *RR-interval* increased, it characterized parasympathetic input (DC; lozenge symbols in Figure 2). Conversely, a sympathetic effect on the cardiac cycle length was represented whenever the *RR-interval* decreased relatively to the previous one, and AC interval was defined (AC; represented by circle symbols in Figure 2). After *RR-intervals* classification, RT^A intervals histograms were built, respectively, following the correspondent *RR-intervals* phases: $RT^A_{\,AC}$ derived from $RR_{\,AC}$ and $RT^A_{\,DC}$ from RR_{DC} intervals.

Statistical analysis

RT^A and *RR* of each subject were pooled and averaged in a class-by-class basis in Controls and Athletes groups, and compared intergroup by non-paired Student *t*-test. Kruskal-Wallis ANOVA was employed to compare *VRD* inter classes. The RT^A length and its variability (MRT^A and $RMS\text{-}RT^A$) was analyzed employing all beats as well as beats selected from AC and DC phases, $MRT^A_{\,AC}$, $MRT^A_{\,DC}$, $RMS\text{-}RT^A_{\,AC}$ and $RMS\text{-}RT^A_{\,DC}$, respectively. Regression lines of *MRR* vs. MRT^A, and $RMS\text{-}RT^A$, were analyzed and angular coefficients (slope) compared between Controls and Athletes groups using non-paired Student t-test. Correlation coefficients (*r*) were assessed by Pearson correlation tests. All tests considered the significance level $\alpha < 0.05$.

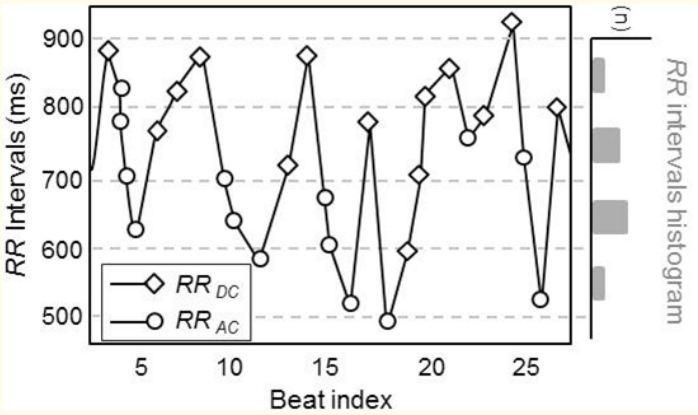

Figure 2: *Acceleration (RR_{AC}) and Deceleration (RR_{DC}) anchor points are represented in RR-intervals samples derived from an ECG recording. RR-interval histogram is represented on the right.*

Results

Linear correlation coefficient (*r*) and respective angular coefficient (*slope*) of regression lines between *MRR* and other each pooled MRT^A and $RMS\text{-}RT^A$ variables in both AC and DC phases are presented in Table 2. The *r values* were significant for all regression lines except in Control group for $RMS\text{-}RT^A$. No intergroup slopes differences were observed for all comparisons ($p > 0.05$).

		MRR vs. MRTA		MRR vs. RMS-RTA	
		Control	**Athletes**	**Control**	**Athletes**
AC	r	0.98*	0.99*	-0.09	-0.95*
	slope	0.0933	0.1112	-0.0007	-0.0075
DC	r	0.98*	0.99*	-0.32	-0.97*
	slope	0.0981	0.1169	-0.0016	-0.0053

Table 2: *Correlation and slopes of pooled mean RR-interval (MRR) vs. pooled mean ventricular repolarization parameters (MRT^A and $RMS\text{-}RT^A$) in AC and DC phases: * $p < 0.05$, RMS: pooled root-mean-squared.*

The pooled MRT^A_{AC} and MRT^A_{DC} were presented for each group, respectively, in figure 3 (a) and (b), as a function of pooled *MRR*. MRT^A showed significant difference between groups for all *MRR* classes ($p < 0.05$).

The MRT^A showed no significant intra-group differences between AC and DC phase, in all *MRR* classes ($p > 0.05$). The interclasses comparison of MRTA variables showed significant difference in both groups *($p < 0.05$, Figure 3 (a) and (b))*.

The pooled $RMS\text{-}RT^A_{AC}$ and $RMS\text{-}RT^A_{DC}$ were presented for Athletes group in figure 4, as a function of *MRR*. The slopes showed no significant difference between AC and DC phases (*p > 0.05*). In Control group, no significant linear correlation (*r*) between *MRR* and $RMS\text{-}MRT^A$ was found.

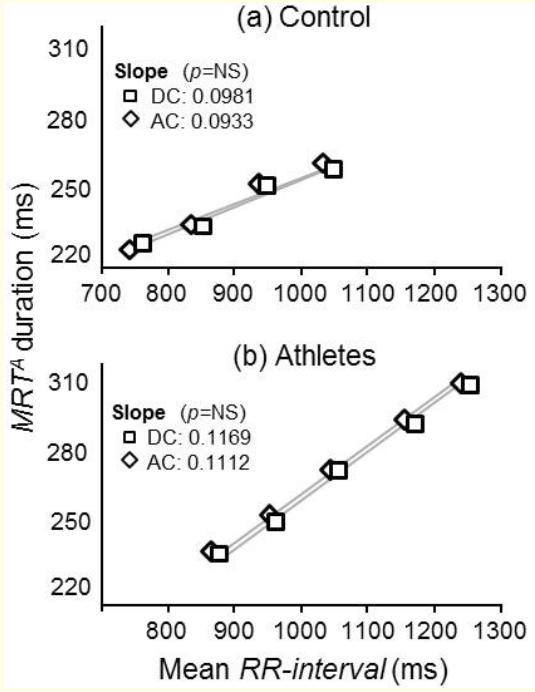

Figure 3: *Pooled MRT^A phase analyses (AC and DC) for (a) Control and (b) Athletes groups as a function of RR-intervals. Note that slopes in Athletes group are steeper than in Control group in AC and DC phases.*

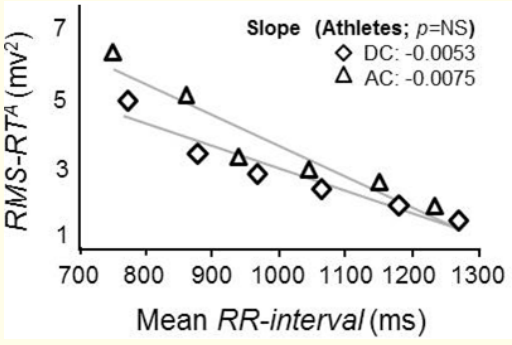

Figure 4: *Pooled RMS-RT^A $_{AC}$ and RMS-RT^A $_{DC}$ as a function of of RR-intervals and respective slopes in Athletes groups. Linear regression lines in AC and DC phases indicate an inverse dependence of RT^A variability vs. RR-interval duration.*

Based on the total number of *RR-intervals* suiting a particular histogram class, the percent value (mean ± SD) of *RR-intervals* pairs rejected as either one not pertaining to the same histogram class was 30.9% ± 10.5% for the Control group and 50.5% ± 16.5% for Athletes. Figure 5 shows *RR-interval* pairs histograms for each group.

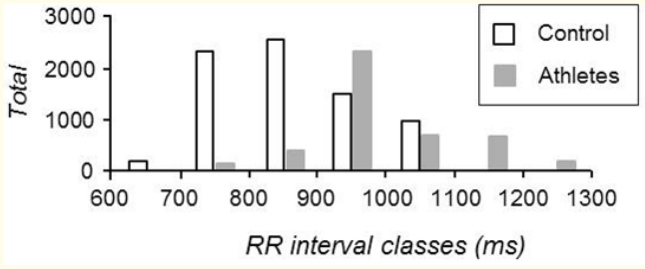

Figure 5: *Histograms of RR-interval-pairs analyzed for Control and Athletes groups. (see text for details)*

Discussion

This study applied a computerized method to automatically analyze the relation between VRD and cardiac cycle length in high performance athletes and healthy sedentary controls. Utilization of RT^{A} interval as a measure of VRD instead of the conventional *QT interval* has been proved to be feasible and has several advantages [14,15]. Most important, RT^{A} is easily identified in the majority of the cases because it is limited by two sharp edges of the ECG (the R- and the T-wave apexes). The conventional *QT interval* requires accurate identification of the *Q-wave* and the *T-wave* offset, and the latter is subject to controversies related to optimal definition of reference offset point in visual identification processes and to adequacy of automated computer algorithms [14]. The increased accuracy in the VRD measurement based on RT^{A} definition, on the other hand, allows the application of non-interactive software [14]. Furthermore, it has been demonstrated that most of both VRD variability and coherence to *RR-interval* series is concentrated in the first portion of the *QT interval* (ending at *T-wave* apex) [16]. In fact, recent studies indicate that VRD offset assessed either at the peak of the *T-wave* or the inflexion point after the peak show high correlation with the VRD measured at end of the *T-wave*, validating this measurement for more accurate determination of ventricular variability [15,17]. The RT^{A} calculation by adjusting the parabola to determine the peak of the *T-wave* has been previously presented and shown to preserve VRD variability accuracy [11].

The *QT interval* reflects the time window extending from the onset of the ventricular activation to the offset of repolarization. Particularly, abnormal repolarization syndromes are often expressed as extreme T-wave form variation and/or prolongation and all of them are associated with life-threatening heart rhythm disturbances [17,18]. However, the determination of abnormal *QT interval* is challenging due to the frequent lack of differentiation of the end of the *T-wave*. Furthermore, it undergoes dynamic variations depending on age, instantaneous HR, autonomic status, medications, etc [17].

In both athletes and healthy sedentary subjects, *QT interval* duration shows significant dependence on the corresponding cardiac cycle length [8]. Additionally, the autonomic nervous system, by vagal tonus predominance (parasympathetic), may also cause *QT interval* to prolong, and increase its temporal dispersion in well-conditioned subjects [9]. In elite athletes, besides the vagal tonus predominance and, consequently, resting bradycardia, which increase the absolute values of *QT interval* duration [19], an increase in left ventricular mass is considered to be an otherwise benign physiological phenomenon, also known as "athlete's heart". Thus, an isolated slightly prolonged *QT interval* in athletes may reflect delayed repolarization as a result of increased ventricular wall thickness [20] and/or slow heart rates [21]. Thus, the analysis of autonomic contributions to VRD dependence may be a valuable tool to assess VRD adaptation to cardiac cycle length in this population.

Because of the substantial inter-subject variability of the QT/*RR-interval* ratio, no mathematical formula holds true for a definite and accurate correction regarding HR status. Consequently, a *RR-interval* correction formula that performs well in one subject may overcorrect or under correct the *QT interval* in other [21]. Hence, the present study relates VRDs to respective *RR-interval*s, preserving the first from correction formulas and allowing more unbiased comparison between healthy subjects and athletes.

The behavior of VRD was analyzed by grouping RT^A interval lengths according to the histogram classes of normal *RR-intervals*. This procedure made it possible to cluster beats expected to bear similar influences due to instantaneous time factors. Additionally, RR series were appropriately isolated of distinguish autonomic contribution on HR variability (HRV), by assessing the capability of the heart to accelerate or to decelerate, respectively, sympathetic (AC phase) and parasympathetic (DC phase) contributions.

The *RR-interval* phase-based processing has been successfully employed in previous studies to assess cardiac vagal modulation by phase-rectified signal averaging (*PRSA*) procedure [10,12]. The technique has been shown to be effective in distinguishing athletes from sedentary healthy volunteers. It hypothesized that depending on vagal stimulus intensity, the rate of ascends of the *RR-interval* series would change accordingly, determining slope variation. Thus, a strongest vagal stimulus would determine a steepest slope and vice-versa, affecting the DC measure.

In both groups, the mean VRD measures were strongly dependent on the instantaneous *RR-interval*, confirming previous findings [11,22]. In a physiological range of variability (700 to 1300 ms), pooled MRT^A are greater at larger *MRR* intervals (Figure 3). This relation held a strong linear dependence ($r > 0.98$; Table 2). MRT^A intra group comparison between AC and DC phases showed no significant differences either in Controls or in Athletes. Thus, it was not possible to isolate any potential hysteresis in VRD adaptation using histogram approach, in the *RR-interval* range analyzed, indicating that beats under a particular *RR-interval* class showed similar repolarization duration regardless cardiac phase. Because AC phase corresponded to sympathetic and DC phase to parasympathetic inputs of the *RR-interval*, based on current data, autonomic phase did not significantly impact repolarization duration in addition to *RR-interval* class itself, in the analyzed range.

On the other hand, beat-to-beat VRD variability has been considered a measure of ventricular autonomic modulation and has prognostic implications [22-25]. In the present study, VRD variability was assessed by root-mean-squared of consecutive RT^A intervals ($RMS\text{-}RT^A$) in AC and DC phases using the *RR-interval* histogram approach. In athletes group, $RMS\text{-}RT^A$ showed an inverse linear relation with *RR-interval* class, in both phases, evidencing that VRD variability increased as *RR-interval* decreased and vice-versa (Figure 4). Although this inverse relation has been previously reported by Barbosa., *et al* [11], to the best of our knowledge, this is the first report of the phenomenon in high performance athletes. Although the interpretation of those observations may seem elusive, reduction of VRD variability as *RR-interval* increases clearly points to a beneficial effect of physical conditioning on ventricular repolarisation stabilization. Those observations were not clearly evident among Controls (Data not shown).

RR-interval pairs in both groups (Figure 5) were frequently placed in classes ranging from 800 to 1100 ms, allowing appropriate class-by-class comparison. Additionally, a larger total number of *RR-interval* pairs were rejected in Athletes than in Controls, as consecutive intervals not pertaining to the same class were expected to occur due to larger inter-cycle length variation in the formers.

Study limitations include:

1. Small sample size,
2. Two physiologically well-defined groups,
3. VO_{2MAX} was estimated indirectly,
4. Groups were loosely matched by age.

It should be emphasized that the present method has not been tested as a risk stratification tool for clinical conditions related to arrhythmias, particularly in athletes. The ability of the method to assess the *RR-interval* to VRD relationship needs further assessments in different clinical settings.

Conclusion

Using RR-interval histogram-based approach, VRD shows linear dependence on *RR-interval* in both healthy sedentary and high performance athletes. This dependence shows no remarkable differences between acceleration and deceleration phases.

Additionally, VRD in athletes is slightly larger than in healthy sedentary volunteers for equivalent *RR-interval* classes. Among athletes, beat-to-beat VRD variability shows an inverse relation to *RR-interval* duration, indicating a potential beneficial of physical fitness on ventricular repolarisation stabilization.

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Conflict of Interest

No financial interest or any conflict of interest exists.

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