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Evaluating Cardiac Vagal Activity on a Conventional Electrocardiogram

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Summary

Objective: To determine the viability of using a conventional electrocardiogram (ECG) tracing for assessment of CVA.

Methods: We retrospectively analyzed 1395 individuals (995 males), aged 46 ± 17.2 years (mean ± standard deviation) with conventional ECG tracings to measure the delta RR (which represents the difference in milliseconds (ms) between the greatest and smallest RR interval) and results of a second autonomic parasympathetic evaluation, the 4-second exercise test (T4s), that quantifies CVA by the cardiac vagal index (CVI). ROC curves were obtained to determine the values of Delta RR for a closer correlation with sensitivity and specificity for 1.20 and 1.95 ms, the low and high CVA cutoff points, respectively.

Results: The delta RR levels correlated significantly with those of the CVI (r=0.40; p<0.001). We identified ≤ 60 and ≥ 120 ms as the best cutoff points for low and high CVA. Sensitivity was 75% and 57%, specificity was 62% and 79%, and the areas of the ROC curves were 0.76 and 0.74, respectively.

Conclusion: The visual measurement of delta RR on an ECG tracing seems to be a valid quick preliminary clinical evaluation of CVA and can be useful in medical offices, emergency units, or situations in which the use of more sophisticated methods may not be feasible, appropriate, or convenient.

Key word: Exercise test, electrocardiography, heart rate.

Introduction

An adverse autonomic condition is frequently associated with a greater mortality risk due to cardiovascular causes and all causality[1-4], primarily because of a decrease in cardiac vagal activity (CVA)[1,5-7]. This lower vago-dependent cardioprotection can be evaluated by the different heart rate (HR) behaviors, such as in situations of rest[2] and exercise[8-10]. Therefore, HR modulation has been widely used as a tool for analysis of the CVA, and is considered a potent and independent prognostic indicator of mortality[11].

In clinical practice, CVA can be measured by different procedures such as heart rate variability (HRV) in the domains of time and frequency, on short and long electrocardiograph (ECG) tracings, by baroreflex sensitivity (BRS)[12], and by diverse maneuvers such as respiratory sinus arrhythmia (RSA)[13] and the initial and final transients of an exercise[14,15]. In this perspective, Araújo et al[16] proposed and validated a protocol called the 4-second exercise test (T4s) in order to evaluate, both reflectively and isolatedly, the CVA by means of the initial HR transient in a sudden dynamic exercise carried out under controlled respiratory conditions, expressed adimensionally by the cardiac vagal index (CVI). This pharmacologically validated[16]

and highly reliable[17] test has been increasingly applied in areas of clinical research and exercise medicine, proving extremely useful not only as a diagnostic tool[18,19], but as a longitudinal follow-up of CVA[20] as well.

Several research groups[17,21-23] have already showed that the reduction of the CVA, measured by HRV, is the main predictor of complex arrhythmias such as sustained ventricular tachycardia, in a 24-hour ECG[24], and even precedes episodes of sudden death[25]. However, the possibility of evaluating the CVA based on simple visual measurements of the duration of RR intervals on short conventional electrocardiographic tracings at rest, with no control of the respiratory pattern or influence of specific respiratory maneuvers, is not known.

The objective of this study was to test the viability of using conventional 10-second ECG tracings to assess the CVA, observing its sensitivity and specificity regarding CVI.

Methods

Sample - We retrospectively analyzed data from 1395 individuals evaluated at our laboratory between 2002 and 2006. We opted for an large heterogeneous sample in order to increase the external validity of our study. A description of the sample is presented on Table 1. Intentionally excluded from our study were individuals with chronic atrial fibrillation and cardiac pacemakers who regularly used negative chronotropic effect medications.

Table 1 - Sample description					
	Total	**Asymptomatic non-athletes**	**CAD**	**Other diseases**	**Athletes**
	(n = 1395)	**(n = 437)**	**(n = 100)**	**(n=745)**	**(n = 113)**
Male	995	322	90	487	96
Female	400	115	10	258	17
Age (years)	46 ± 17.17	39 ± 15.26	65 ± 10.90	51 ± 14.84	26 ± 9.80
	(9-91)	(9-84)	(38-91)	(10-90)	(11-55)
Weight (kg)	76.4 ± 16.48	74.0 ± 13.88	79.3 ± 13.44	77.9 ± 18.51	73.2 ± 11.8
	(34.7-170.0)	(36.9-122.0)	(46.8-122.0)	(36.6-170.0)	(34.7-105.9)
Height (m)	1.71 ± 0.1	1.72 ± 0.1	1.71 ± 0.1	1.69 ± 0.1	1.77 ± 0.1
	(1.28-2.06)	(1.36-2.03)	(1.48-1.86)	(1.28-1.94)	(1.39-2.06)
CVI	1.49 ± 0.29	1.57 ± 0.27	1.29 ± 0.17	1.43 ± 0.27	1.74 ± 0.28
	(1.01-3.25)	(1.05-2.67)	(1.01-2.07)	(1.03-3.25)	(1.18-2.56)
Delta RR (ms)	105 ± 90.92	123 ± 101.1	61 ± 51.15	89 ± 72.61	176 ± 126.43
	(10-1000)	(10-1000)	(10-260)	(20-680)	(20-660)

CAD - coronary artery disease; age, CVI - cardiac vagal index and delta RR- maximum and minimum RR intervals in 10 ms of an electrocardiogram – values expressed as mean ± standard deviation (minimum – maximum).

All subjects evaluated were voluntarily submitted to an exercise medicine assessment geared towards a clinical diagnosis or physical exercise orientation. This appraisal was comprised of a clinical visit that included a detailed medical history and physical examination, a conventional resting electrocardiogram, a 4-second exercise test (T4s), spirometry test and a maximal exercise cardiopulmonary test, all carried out during the same visit and in this order.

Additionally, before any of the procedures took place, subjects read and signed an informed consent form that had been previously approved by the Research Ethics Committee. Most subjects were light-skinned and came from a high socioeconomic bracket.

The 4-second exercise test - The T4s was pharmacologically validated[16] for an isolated evaluation of the integrity of the CVA through analysis of the initial HR transient (resting-exercise transition), and had already been used in studies conducted by our group[16,26] and by other researchers[27]. The T4s consists of pedaling as fast as possible on a lower-limb cycle-ergometer (Cateye EC-1600, Cat Eye, Japan) with no load, from the 4th to the 8th second of a 12-second maximal inspiratory apnea. During the T4s test, the patient's feet are affixed to the pedals with toe clips. Under electrocardiographic monitoring (Elite Ergo PC 3.1.2.5, Micromed, Brazil) of one lead, generally CM5 or CC5, certain RR intervals are visually identified and subsequently measured during the maneuver with the help of software resources, using a 10 ms resolution. The T4s quantifies the CVA by means of the CVI, which represents the heart rate acceleration reflectively triggered by vagal cardiac inhibition. The CVI is expressed by the ratio between the RR interval immediately before exercise or the first RR interval of the exercise, whichever is longest (RRB), and the shortest RR interval during exercise (RRC). Generally, two maneuvers are performed, and the one that provides the greater CVI value is chosen. A more detailed explanation of the method may be found in a publication by our research group[28].

Delta RR measurement (conventional ECG) - We obtained the measurement of delta RR, based on a resting 10-second ECG (Schiller Cardiovit AT 10, Switzerland) in the supine position, with no respiratory control, after the patient had been at rest, by observing the long DII lead, at a 25 mm/s paper speed.

The delta RR on this tracing, expressed in ms, was obtained by the difference between the longest and the shortest RR intervals contained in this recording, excluding extrasystole or escape rhythm. The RR intervals were measured visually (sometimes with the aid of a millimeter lens) by a trained physician, using a 10 ms resolution (0.25 mm), before he was informed of the T4s result.

Statistics and data analysis procedure - Initially, normality and homoscedasticity of distribution were tested, validating the use of parametric statistics. In order to assess the association between the variables analyzed, we used Pearson's product-moment correlation. The sample was subdivided into three subgroups according to the CVA measured on the T4s by the CVI cutoff points (≤ 1.20, between 1.21 and 1.94, and ≥ 1.95) and variance analysis was used to observe the differences between the means of delta RR among the three subgroups, followed by Bonferroni *post hoc* comparisons, whenever appropriate.

The ROC curves were calculated in order to determine the values of delta RR with the best sensitivity and specificity for the proposed cutoff points for a high and low CVA, respectively, CVIs of 1.20 and 1.95. The lower cutoff point was based on previous studies at our laboratory[9,17], while the upper cutoff point was based on the 95th percentile for CVI in the young (between 18 and 35 years of age) and healthy sample of the extensive database of our laboratory. The analyses were performed with the SPSS statistics software, 13.0 version,

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USA, except for the ROC curves that were calculated using Medcalc 7.3.0.1 version software, Belgium. Financial support was provided by the CNPq and FAPERJ.

Results

The values of delta RR showed a significant correlation with the CVI (r=0.40; p<0.001). Based on the cutoff points used for the CVI, 199 individuals were classified as having low CVA and 106 as having high CVA. When stratified by sample characteristics, we found that among the 113 athletes, only one had low CVA, and among the 100 subjects with CAD, only three had elevated CVA.
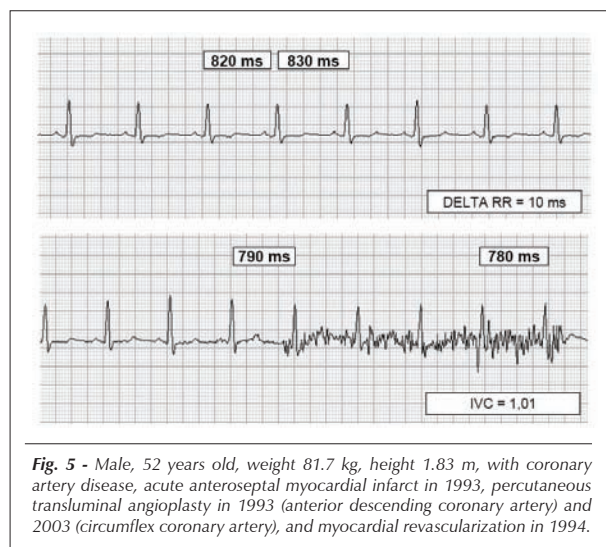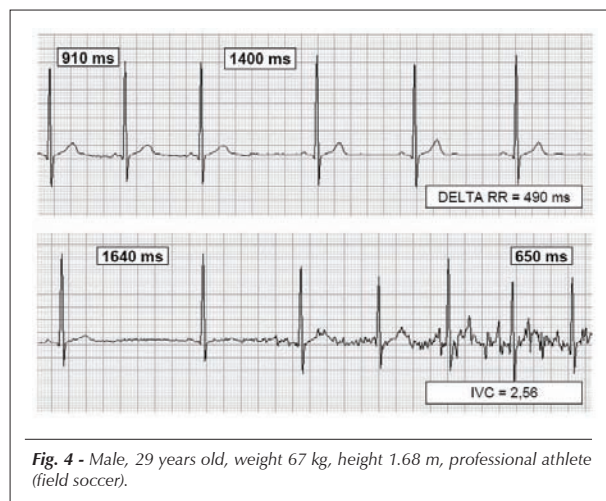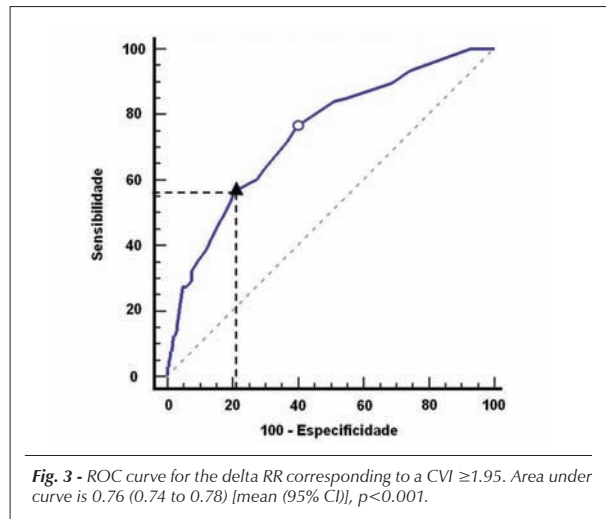
The values of the delta RR in ms, expressed as means (95% CI) in the three groups were 57 (51 - 63), 105 (100 - 110), and 188 (159 - 218). The results of the variance analysis and of the Bonferroni *post hoc* comparisons are shown on Figure 1.

Analyzing the ROC curves, we identified ≤ 60 and ≥ 120 ms as the best cutoff points corresponding to the low (CVI ≤ 1.20) and high (CVI ≥ 1.95) CVAs, with sensitivity levels of 75% and 57%, and specificity levels of 62% and 79%,
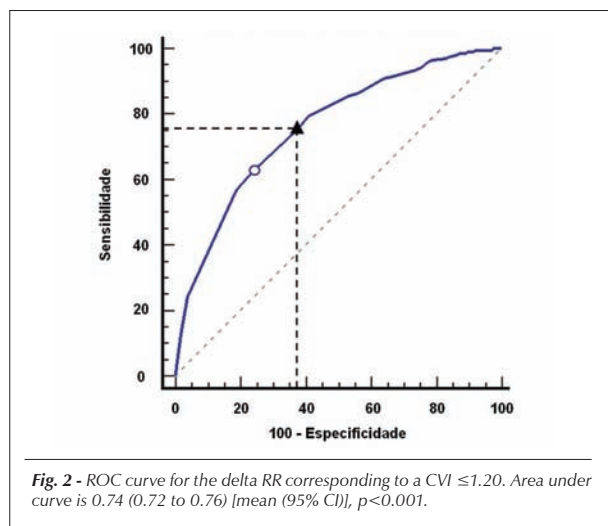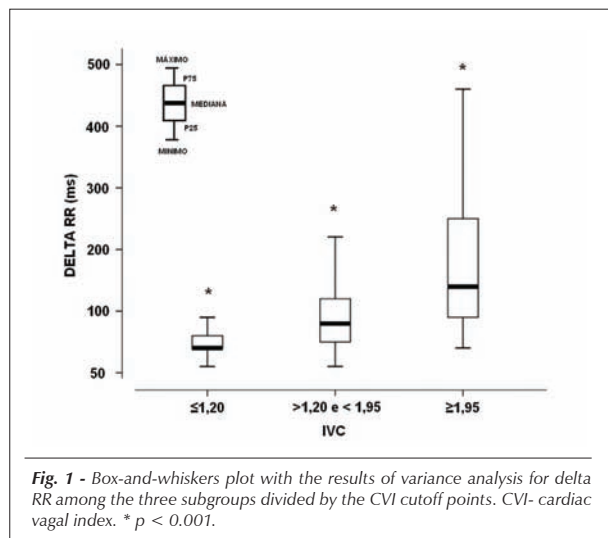
respectively. Curves and their respective areas are shown on Figures 2 and 3.

Figures 4 and 5 illustrate the resting ECG tracings,

Fig. 3 - ROC curve for the delta RR corresponding to a CVI ≥1.95. Area under curve is 0.76 (0.74 to 0.78) [mean (95% CI)], p<0.001.

Fig. 1 - Box-and-whiskers plot with the results of variance analysis for delta RR among the three subgroups divided by the CVI cutoff points. CVI- cardiac vagal index. * p < 0.001.

Fig. 4 - Male, 29 years old, weight 67 kg, height 1.68 m, professional athlete (field soccer).

Fig. 2 - ROC curve for the delta RR corresponding to a CVI ≤1.20. Area under curve is 0.74 (0.72 to 0.76) [mean (95% CI)], p<0.001.

Fig. 5 - Male, 52 years old, weight 81.7 kg, height 1.83 m, with coronary artery disease, acute anteroseptal myocardial infarct in 1993, percutaneous transluminal angioplasty in 1993 (anterior descending coronary artery) and 2003 (circumflex coronary artery), and myocardial revascularization in 1994.

with measurements of delta RR, and of the T4s, with the measurement of the CVI, from two typical cases, one with a low CVA and the other with a high CVA.

Discussion

The rapid HR transient at the beginning of a passive[29] or active exercise occurs exclusively by vagal removal, as was pharmacologically validated by Araújo et al[16]; it is the physiological basis of the T4s. We know that the magnitude and part of the variability of the resting HR depend on the parasympathetic branch of the autonomic nervous system. Although they represent distinct physiological moments of autonomic activity, we noted an association between results found with these two methods for CVA evaluation.

In scientific literature we observe the proposition of diagnostic methods habitually stemming from the results obtained by ROC curves, considering as valid a method with a curve area greater than 0.50[30]. Additionally, the levels obtained for sensitivity and specificity of the method proposed have great clinical relevance. Roche et al[31] noted that the reduction in HR variability in the time domain is a valid screening tool for the sleep apnea syndrome, with results of 89.7% in sensitivity and 98.1% in specificity.

In the past, the RSA was the most utilized method for CVA evaluation. The difference was measured between the RR intervals in distinct respiratory maneuvers. However, some years ago, Piepoli et al[32] showed that the RSA could be modified according to the baroreflex stimulation of arterial receptors, thus leading to the development and implementation of new methods.

At present, the main studies on the theme use spectral analysis methods with measurements in the time or frequency domains[33], graphics of Poincaré, analysis of heart rate turbulence[34], and fractal analysis[24]. Nonetheless, there are significant methodological differences, and some showed conflicting results that allowed criticism of the referred methods, such as that by Goldberger et al[35], who suggested that the baseline level of parasympathetic activity and the stimulus intensity determine the magnitude of the HR variability, by the effect observed in the sinus node. In fact, considering the multiplicity of factors that interfere in the autonomic components and are practically impossible to control by a 24-hour tracing, this makes the interpretation of these analyses even more difficult and limits their clinical use.

In a prior investigation conducted by specialists[36], the presence of RSA in a resting ECG was considered one of the criteria of greatest suspicion for an increased CVA. Thus, the objective of this research was to propose a simple, quick, non-invasive, and extremely practical strategy for the evaluation of CVA based on a conventional ECG tracing in emergency rooms, rescue vehicles, medical offices, or even non-medical environments such as sports arenas, home care, or airports.

An earlier study by our research group[37] identified an important correlation between the CVI and the duration of RR intervals on a resting ECG in athletes. Seeking to identify an electrocardiographic criterion for vagotonia, we used the ROC curve, showing that a mean of RR intervals over 990 ms would have sufficient accuracy (75%) to identify vagotonia, which was defined in that study as a CVI over 2.0 because of the smaller sample and the exclusive participation of athletes.

Our results corroborated the impression of a significant association between the CVI and the delta RR measurement on a resting ECG tracing without respiratory maneuvers in an intentionally ample and heterogeneous sample, encompassing healthy and non-healthy adults and athletes. This suggests that the information provided by this measurement is clinically relevant and may have wide practical applicability. We further note that the values proposed by the ROC curves for delta RR proved very robust for the populational extremes, i.e., subjects with CAD and healthy subjects, as shown in the results.

A practical question could be asked regarding the delta RR measurement. Is it necessary and feasible to measure with a 10 ms resolution in emergency situations? Considering that high and low CVAs are represented by 60 and 120 ms, respectively, it is simple to visually distinguish and measure these values (1.5 and 3 mm) on a long DII tracing, thus allowing an easy estimate of the CVA in several circumstances of the medical practice, even without carefully measuring the delta RR with the resolution adopted in our analysis.

We recognize, however, that control difficulties in producing an ECG tracing such as the time of decubitus, absence of noise, and the emotional state of the individuals analyzed, may constitute limitations to the external validity of the study. Nevertheless, considering the wide use of an ECG tracing in different clinical situations and the simplicity of the method we present, in contrast to the complexity of other methods currently available for the same purpose, we recognize the potential of the delta RR measurement as a practical method for a preliminary clinical evaluation of CVA.

We conclude that the visual measurement of delta RR in 10s of an ECG tracing in one single lead seems to be a valid tool for a simple and low-cost preliminary estimate of cardiac vagal integrity; this may prove to be potentially useful in situations where more sophisticated methods of autonomic evaluation may not be feasible, timely or convenient.

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