High-resolution electrocardiography in the diagnosis of arrhythmogenic right ventricular cardiomyopathy in Boxer dogs

Eletrocardiografia de alta resolução no diagnóstico da cardiomiopatia arritmogênica do ventrículo direito em cães da raça Boxer

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ABSTRACT

To evaluate the reliability of high-resolution electrocardiography in the diagnosis of arrhythmogenic right ventricular cardiomyopathy in Boxers, 20 dogs with no structural cardiac alterations at echocardiographic examination were grouped on the basis of frequency of ventricular arrhythmias, evaluated by 24-hour ambulatory ECG, and undergoing a high-resolution electrocardiography. High frequency QRS duration, duration of terminal QRS complex less than 40µV (LAS40) and root mean square voltage of the terminal 40 milliseconds of the QRS complex (RMS40) were measured. Differences in high-resolution ECG variables were not observed between groups. Therefore, the results of this investigation suggest that high-resolution electrocardiography is not a useful method for the diagnosis of arrhythmogenic right ventricular cardiomyopathy in Boxers without detectable myocardial alterations or systolic dysfunction.

Key words: late potential, ventricular arrhythmia, dog.

RESUMO

Com o objetivo de avaliar a importância da eletrocardiografia de alta resolução no diagnóstico da cardiomiopatia arritmogênica do ventrículo direito do Boxer, 20 cães sem evidências de doença cardíaca estrutural à avaliação ecodopplercardiográfica foram agrupados de acordo com a frequência de arritmias ventriculares, avaliadas pela eletrocardiografia ambulatorial de 24 horas, e submetidos ao exame eletrocardiográfico de alta resolução. Duração do complexo QRS filtrado, duração dos sinais de baixa amplitude (menor que 40µV) dos últimos 40 milissegundos do complexo QRS e raiz quadrada média da voltagem ao quadrado dos últimos 40 milissegundos do complexo QRS (RMS40) foram as variáveis avaliadas. Não foram observadas diferenças significativas entre os grupos em relação às variáveis estudadas. Sendo assim, os resultados do presente estudo sugerem que a eletrocardiografia de alta resolução não é uma ferramenta útil no auxílio diagnóstico da cardiomiopatia arritmogênica do ventrículo direito dos cães da raça Boxer que não apresentam alterações miocárdicas evidentes ou disfunção sistólica.

Palavras-chave: potencial tardio, arritmia ventricular, cães.

INTRODUCTION

Boxer arrhythmogenic right ventricular cardiomyopathy (ARVC) is inherited as an autosomal dominant disease with incomplete penetrance that can lead to syncope or sudden death as consequence of ventricular arrhythmias resulting from ultrastructural changes in cardiomyocytes that modifies the electrical and mechanical cell activity (MEURS, 2004; OYAMA et al., 2008; MEURS, 2010; OXFORD et al., 2011).

The diagnostic tools currently used rely on the presence of such arrhythmias for the identification of affected individuals. However, it is not common practice to check for the presence of an anatomic arrhythmogenic substrate generated by characteristic fibrofatty infiltrates, which is implicated as a causative factor of ventricular arrhythmias in this disease (SPIER & MEURS, 2004). This inability to identify myocardial alterations which may be related to the genesis of ventricular arrhythmias makes early diagnosis of ARVC difficult.

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High-resolution electrocardiography (HRECG) is a noninvasive method which allows detection of arrhythmogenic substrates by identification of late potentials defined as high-frequency, low-amplitude delayed electrical signals which are present in the terminal portion of the QRS complex and extend into the ST segment (SANTANGELI et al., 2008).

It is possible that HRECG could detect anatomic arrhythmogenic substrates generated by fibrofatty infiltrates in dogs affected by ARVC, even in patients with low number of ventricular arrhythmias. This would make HRECG an additional tool to diagnose ARVC and predict the development of arrhythmias in dogs affected by this disease. Therefore, the aim of present study was to evaluate the efficacy of HRECG in the diagnosis of ARVC in Boxer dogs.

MATERIAL AND METHODS

Patient selection criteria

Client-owned Boxer dogs aged 4 years and up were recruited for a prospective study. Exclusion criteria included any alteration in the physical exam, congenital heart disease, valve insufficiency and systolic or diastolic dysfunction such as increased cardiac dimension at the echocardiographic evaluation. Dogs with right or left bundle branch block at the electrocardiographic screening test or those receiving antiarrhythmic drugs were also excluded.

Patient grouping

Patients were distributed into three groups according to their frequency of ventricular premature complexes (VPCs) as observed at 24-hour ambulatory electrocardiogram (Holter monitoring), performed one day before HRECG. Animals which exhibited less than 20VPCs/24 hours were included in the control group (GC). Those which exhibited between 100 and 999 VPCs/24 hours were classified as probably affected by ARVC and included in the second group (GD1). Dogs which exhibited over 1000 VPCs/24 hours were also classified as probably affected and were included in a third group (GD2). Categorization of the dogs was performed according to MEURS (2010).

High resolution electrocardiography (HRECG)

HRECG was performed in propofol-anesthetized dogs according to the recommendations of FERREIRA et al. (2005) to facilitate execution of the exam and reduce electrocardiographic noise to acceptable levels, that is, <0.7µV. Patients with electrocardiographic noise values higher than that were excluded from the study.

Animals were maintained in left lateral recumbency and electrodes were placed on shaved areas of the body surface. Leads were placed as follows: on the 6th intercostal space on the right (negative electrode) and left (positive electrode) sides of the thorax at the level of the costochondral junction (X axis); on the manubrium (negative electrode) and xiphoid process area (positive electrode) (Y axis); and above the spinous process of 7th thoracic vertebrae (negative electrode) and the ventral opposite aspect (positive electrode) (Z axis).

Signals digitally filtered with bidirectional filters (40Hz to 250Hz) were recorded by digital device[a] and processed by specific software[b]. The signals were combined into a vector magnitude waveform ($\sqrt{X2+Y2+Z2}$). This vector magnitude composite was used to measure filtered QRS duration (QRS), duration of low-amplitude signal (LAS) below 40µV and root mean square voltage of the last 40 milliseconds (ms) of the QRS (RMS40). Exams with 2 or more of the following criteria were considered positive for late potentials: 1) QRS>75ms; 2) LAS40>26ms; 3) RMS40<117µV. The diagnostic performance of only 1 abnormal parameter was also tested.

Data analyses

Data were submitted to Cramer-von Mise normality test and One-Way ANOVA. The Fisher's exact test was used to compare the percentage of abnormal HRECG parameters and prevalence of positive exams between groups.

Sensitivity, specificity, positive predictive value and negative predictive value of HRECG for the diagnosis of ARVC were also calculated, with results of > 100VPCs at 24-hour ambulatory electrocardiogram used as reference. For each test, differences were considered significant when P<0.05. The SAS system for Windows, version 9.0 was used to perform the statistical analyses.

RESULTS

Twenty client-owned Boxer dogs were enrolled in the study. Out of these 20 dogs, 15 (75%) were female and 5 (25%) were male. The control group (GC) comprised 10 Boxers (7 females and 3 males), with ages ranging from 4 to 10 years (mean of 6.2 years) and less than 20VPCs/24 hours (mean

of 8.4VPCs/24 hours). The second group (GD1) had 5 female Boxers with ages ranging from 5 to 11 years (mean of 8 years) and number of VPCs between 109 and 959VPCs/24 hours (mean of 402VPCs/24 hours). The third group (GD2) had 5 Boxers (3 females and 2 males) with ages ranging from 6 to 12 years (mean of 9.4 years) and numbers of VPCs/24 hours between 1004 and 13850 (mean of 4403VPCs/24 hours).

None of the studied animals exhibited clinical signs of hemodynamic instability caused by ventricular arrhythmias.

Ventricular bigeminy and trigeminy were commonly observed. The dogs also exhibited isolated, couplet and triplet VPCs, although paroxysmal ventricular tachycardia was the most severe rhythm observed. None of the animals exhibited sustained ventricular tachycardia.

Descriptive data for QRS, LAS40 and RMS40 for all three groups are shown in table 1. Number and percentage of each abnormal variable as well as the number of positive exams were also tabulated (Table 2). Sensitivity, specificity, positive predictive value and negative predictive value of HRECG with 1 and 2 or more abnormal parameters are shown in table 3.

DISCUSSION

It is well know that the diagnostic value of HRECG for human patients with mild forms of ARVC is poor, only about 30% of these patients exhibit late potentials (NAVA et al., 2000). In the present study, to exclude animals with dilated cardiomyopathy, only Boxers with no chamber alterations at the echocardiographic evaluation were recruited; therefore, according to the classification proposed by OSELLADORE et al. (1995), the absence of cardiomegaly suggested a minor cardiac involvement, defining the minor form of the disease.

Thus, the number of affected individual (GD1+GD2) with the so called mild form of the disease which exhibited abnormal HRECG corresponded to 30% of all dogs included in this study, exactly the same percentage of human patients. This data indicates that, at least for the dogs enrolled in this study, a minor myocardial involvement implies a minor delay in the depolarization wave and, consequently, a minor number of alterations in the HRECG exam, as described for human patients with ARVC (OSELLADORE et al., 1995; NAVA et al., 2000).

Conversely, for those patients presenting a severe form of disease, HRECG presents more relevant features. In a study evaluating the role of HRECG in Boxer with ARVC on the basis of systolic function and clinical outcome, the authors observed alterations in almost all tested parameters in patients with congestive heart failure and fractional shortening <20% compared with patients with no clinical signs and fractional shortening >20%, respectively (SPIER & MEURS, 2004). When NAVA et al. (2000) took into account the severity of arrhythmias and the extension of myocardium involvement in human patients with ARVC, they observed alterations in approximately 70% of the patients with ventricular fibrillation or sustained ventricular tachycardia and in almost 100% of the patients with a diffuse form of ventricular involvement. Similarly, TURRINI et al. (1999) observed the most significant alterations in RMS40 in people with sustained ventricular arrhythmias.

Therefore, although it has been shown that HRECG is an important diagnostic tool in patients with severe form of disease (TURRINI et al., 1999; NAVA et al., 2000; SPIER & MEURS, 2004), in this study the high number of false positive and false negative was responsible for the low sensitivity, specificity, positive predictive value and negative predictive value, discarding the test as a diagnostic tool in patients with mild form of disease. Thus is

Table 1 - Values of HRECG parameters (mean ± standard deviation) of non-affected (GC; n=10) and ARVC affected Boxers which exhibited between 100 and 999VPCs/24 hours (GD1; n=5) and over 1000VPCs/24 hours (GD2; n=5).

Parameter	Groups			P value
	G_C	G_{D1}	G_{D2}	
QRS (ms)	80.30 ± 5.20	79.20 ± 6.30	79.20 ± 8.28	0.927
LAS40 (ms)	20.90 ± 4.17	22.00 ± 6.20	21.40 ± 6.02	0.927
RMS40 (µV)	153.80 ± 52.56	124.20 ± 34.77	128.20 ± 44.90	0.438
Noise level(µV)	0.33 ± 0.16	0.38 ± 0.20	0.36 ± 0.20	0.878

P value, significance level of one-way ANOVA;
QRS, filtered QRS duration; LAS40, duration of the low-amplitude signal below 40µV in the last 40 milliseconds of the QRS; RMS40, root mean square voltage of the last 40 milliseconds of the QRS; ms, milliseconds; µV, microvolt.

Table 2 - Number and percentage of each abnormal variable and positive HRECG (≥2 abnormal parameters) of non-affected (GC; n=10) and ARVC affected Boxers which exhibited between 100 and 999VPCs/24 hours (GD1; n=5) and over 1000VPCs/24 hours (GD2; n=5).

Parameter	Groups			P value
	G_C n (%)	G_{D1} n (%)	G_{D2} n (%)	
QRS (ms)	9 (90)	3 (60)	3 (60)	0.22
LAS40 (ms)	2 (20)	1 (20)	1 (20)	1.00
RMS40 (µV)	4 (40)	1 (20)	2 (40)	0.84
Positive HRECG	5 (50)	2 (40)	1 (20)	0.83

P value, significance level of Fisher's exact test;
QRS, filtered QRS duration; LAS40, duration of the low-amplitude signal below 40µV in the last 40 milliseconds of the QRS; RMS40, root mean square voltage of the last 40 milliseconds of the QRS; ms, milliseconds; µV, microvolt.

reasonable to describe the HRECG as a method to assess progression of the disease and myocardial damage rather than a diagnostic method.

However, some of the studied Boxers still exhibited an expressive number of VPCs even when no late potentials were detectable. NAVA et al. (2000) studied humans who exhibited minor forms of ARVC with an expressive number of VPCs and proposed two possibilities to explain their observations in those patients: firstly, that the re-entry circuits, which are supposedly involved in the genesis of arrhythmias, were determined by localized conduction defects not detectable by HRECG; secondly, that such arrhythmias were not caused by re-entry circuits but by automatic foci instead.

With the aim of determining more accurate criteria for the diagnosis of ARVC in human patients, the consideration of only one abnormal parameter instead of two or more has been previously proposed as a way to substantially raise HRECG sensitivity (KAMATH et al., 2011). In the present study, the application of this method did, indeed, increase the sensitivity of the test from 30% to 70%; however, the specificity was reduced from 50% to 10%.

Such a reduction in specificity was a consequence of the high number of false-positive results observed as a consequence of the presence of a high percentage (75%) of animals with QRS duration values higher than those used as normal standards.

Considering that reference values used nowadays have been obtained in a study with Doberman Pincher dogs (CALVERT et al., 1998), it is possible to suggest that abnormal values obtained in the present study may be not abnormal, but characteristic of the Boxer breed instead. This further suggests that normal values currently used are not universal and, for this reason, should be defined for each breed.

One limitation of this study was the small number of dogs. The values of QRS and LAS40 were nearly identical between groups and therefore unlikely that the addition of more animals in each group allows identification of significant differences. However, it can be seen that the group with the largest number of animals (GC) had the greatest number of positive HRECG and RMS40 value slightly greater than those of the other groups, although not significantly. Thus, it is reasonable to assume that the addition of more dogs to affected groups may in some way alter the reliability of the test.

The decision to hold the HRECG in anesthetized animals may be a possible confounding factor. The characteristic panting of Boxer dogs prevented all attempts to acquire signals with

Table 3 - Diagnostic performance of 1 and 2 or more abnormal HRECG parameters for the identification of ARVC in 20 Boxer dogs.

Parameter	Formula	HRECG (1 parameter) % (95% CI)	HRECG (≥2 parameters) % (95% CI)	P value
Sensitivity	TP/(TP + FN) x 100	70 (34.6-93.3)	30.0 (6.7-65.3)	< 0.0001
Specificity	TN/(FP + TN) x 100	10 (0.3-44.5)	50 (18.7-81.3)	< 0.0001
PPV	TP/(TP + FP) x 100	43 (19.8-70.1)	37.5 (8.5-75.5)	0.38
NPV	TN/(TN + FN) x 100	25 (0.6-80.6)	41.7 (15.2-72.3)	0.01

P value: significance level of the Chi-square test;
PPV, positive predictive value; NPV, negative predictive value; TP, true-positive result; TN, true-negative result; FP, false-positive result; FN, false negative result; CI, confidence interval.

acceptable levels of noise. Although it is known that different anesthetic agents can alter the values of HRECG variables, FERREIRA et al. (2005) showed that anesthesia with propofol did not significantly alter these variables.

CONCLUSION

HRECG is not reliable as an ancillary exam for the early diagnosis of ARVC, at least in patients with no detectable signs of myocardial alterations or systolic dysfunction.

BIOETHICS AND BIOSAFETY COMMITTEE APPROVAL

Protocol number 002965/10.

SOURCES OF ACQUISITION

a - Cardioflash® digital – Cardios Sistemas – São Paulo, Brazil.
b - CardioManager® digital – Cardios Sistemas – São Paulo, Brazil.

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