Electrocardiographic markers of myocardial conduction and repolarization in Boxer dogs

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Electrocardiographic markers have been used in people to classify arrhythmogenic risk. The aims of this study were to investigate electrocardiographic markers of conduction and repolarization in Boxers and non-Boxer dogs, and compare such findings between groups. Ten-lead standard electrocardiograms of Boxer dogs and non-Boxers recorded from 2015 to 2018 were retrospectively reviewed. Dogs ≥4 years of age and weighing >20kg were included. Animals with valvular insufficiencies, congenital cardiopathies, cardiac dilation, suspected systolic dysfunction, biphasic T-wave, bundle branch blocks, and those receiving antiarrhythmics were excluded. Electrocardiographic markers of conduction, QRS duration (QRSd) and dispersion (QRSD), and repolarization (corrected QT interval, Tpico-Tfinal, JT and JTpico), as well as derived indices, were measured. Two hundred dogs met the inclusion/exclusion requirements, including 97 Boxers (8.1±2.5 years old; 30±7kg) and 103 non-Boxer (8.8±2.5 years old, 30±8kg). QRSd and QRSD, and repolarization markers in lead II and left precordial lead V4 were considered similar between groups. Dispersion of late repolarization on lead rV2, Tpico-Tfinal interval, was considered longer in Boxers (45±8ms vs 38±10ms, P=0.01). The Tpico-Tfinal/JT and the JTpico/JT also differed between groups. Our results indicate that the dispersion of myocardial late repolarization in lead rV2 is slower in Boxers than other dog breeds.

INDEX TERMS: Electrocardiography, myocardium, conduction, repolarization, Boxer dogs, arrhythmias, canine, electrocardiography, premature cardiac complexes.

RESUMO.- [Marcadores eletrocardiográficos de condução e repolarização miocárdica em cães da raça Boxer.] Marcadores eletrocardiográficos têm sido estudados em seres humanos para estratificação do risco arritmogênico. Os objetivos deste estudo foram investigar os marcadores eletrocardiográficos de condução e repolarização miocárdica em Boxers e em cães de outras raças, e comparar tais resultados entre os grupos. Para tal, a eletrocardiografia convencional de 10 derivações registradas de 2015 a 2018 foram avaliadas de maneira retrospectiva. Cães com idade igual ou superior a 4 anos e pesando >20kg foram incluídos. Animais com insuficiência valvar, cardiopatias congênitas, dilatação cardíaca, suspeita de disfunção sistólica, onda T bifásica, bloqueio(s) de ramo(s), ou aqueles que recebiam antiarrítmicos foram excluídos. Variáveis eletrocardiográficas de condução, como a duração e dispersão do complexo QRS (QRSd e QRSD respectivamente), e repolarização (intervalo QT corrigido, Tpico-Tfinal, JT e JTpico), bem como índices derivados, foram mensurados. Duzentos cães que se adequaram aos critérios de inclusão/exclusão foram incluídos, 97 Boxers (8,1±2,5 anos; 30±7kg) e 103 não Boxers (8,8±2,5 anos; 30±8kg). O QRSd e o QRSD, e os marcadores de repolarização nas derivações II e V4 foram similares entre os grupos. O marcador de dispersão da repolarização tardia na derivação rV2, Tpico-Tfinal foi considerado mais longo no
INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disease commonly seen in adult Boxer dogs. The disease is characterized by the replacement of right ventricle (RV) cardiomyocytes by a fibrofatty tissue, a condition that eventually generates areas prone to the formation of ventricular arrhythmias, which may culminate in sudden death (Harpster 1983, 1991). There is no single and specific diagnostic test for ARVC, thus, in veterinary practice, the diagnosis is best based on a combination of findings which may include: the presence of ventricular tachyarrhythmia with no other documented causes for the arrhythmia, syncope, and family history of ARVC (Meurs 2004, 2017). Although many Boxers with ARVC live for years even without treatment, they are always at an increased risk of sudden cardiac death (Meurs 2017).

In people many electrocardiographic markers have been studied to identify individuals at risk for malignant arrhythmias and sudden death (Kurl et al. 2012, Kurosaki et al. 2013, Tse & Yan 2016, Zumhagen et al. 2016). These can be based on myocardial conduction, such as QRS duration (QRS), which is a surrogate marker of conduction velocity (CV), and QRS dispersion (QRS) reflecting CV dispersion. Conduction abnormalities associated with reduced CV, along with a functional or structural obstacle, are conditions for re-entrant activity (Tse & Yan 2016).

Abnormal repolarization properties can increase the risk of triggered activity and re-entrant arrhythmias, the latter known to be involved in the pathogenesis of ARVC (Basso et al. 2015). Electrocardiographic markers based on repolarization include: corrected QT (QTc), QT dispersion (QTd), interval from the peak to the end of the T-wave (Tpeak-Tend), and interval from J point to the peak and/or end of the T-wave (Jpeak-JT, respectively).

Although studied in many conditions known to be associated with increased arrhythmogenicity in man, such as ARVC (Zorzi et al. 2013), diabetes (Stettler et al. 2007), sepsis (Ozdemir et al. 2016), and myocardial infarction (Zhao et al. 2012), studies investigating electrocardiographic markers of conduction and repolarization in dogs are lacking. The aims of this study were to investigate electrocardiographic markers of conduction and repolarization in Boxers and non-Boxer dogs over 20 kg, and compare such findings between the general population and a breed widely known to be predisposed to developing ventricular arrhythmias.

MATERIALS AND METHODS

Study Design and Ethics Statement. This retrospective study was approved by the institutional Animal Care and Use Committee (protocol 012277/17).

RESULTS

A total of 200 dogs met the inclusion/exclusion requirements and were recruited for this study. The sample comprised 97
Boxers and 103 non-Boxer dogs. No differences in gender were documented within or between groups. The mean body weight did not differ between groups (Boxers 30±7kg, non-Boxers 30±8kg, P=0.82). The mean age was also considered similar between groups (Boxers 8.1±2.5 years old, non-Boxers 8.8±2.5 years old, P=0.16). Among NBG, mixed breed dogs were most represented (n=67, 65%), followed by Labrador Retrievers (n=11, 11%), Pitbulls (n=9, 9%), and Golden Retrievers (n=8, 8%). No animal from NBG had a history of syncope. In BG, nine dogs (9%) had a clinical history of syncope, and 88 (91%) had no previous history.

The electrocardiographic markers of conduction, $QRS_d$ and $QRS_D$, were considered similar between BG and NBG. Also, no differences existed between BG and NBG regarding the myocardial repolarization markers obtained from leads II and V4. When looking at lead rV2, the dispersion of late repolarization evaluated as $T_{peak-T_{end}}$ was longer in Boxers (45±8ms) than in non-Boxer dogs (38±10ms) (P=0.01). Similarly, the dispersion of repolarization normalized to $JT_{peak}$ interval obtained from lead rV2, i.e. $T_{peak-T_{end}}/JT_{peak}$, was found to be higher in BG (0.41 [0.35-0.51]) than in NBG (0.37 [0.27-0.40]) (P=0.03). Curiously, the dispersion of repolarization normalized to JT interval, the $JT_{peak}/JT$, was found to be slightly lower in Boxers (0.72 [0.67-0.75] vs 0.73 [0.71-0.79], P=0.04). Our results are summarized in Table 2, and box-plots of markers found to be different between groups are represented in Figure 2.

Interestingly, no differences were documented in the electrocardiographic markers between syncopal and non-syncopal Boxers (Table 3), or between Boxers considered normal (n=12) and those likely affected by ARVC (n=15) according to the 24-Hour Holter criteria for the degree of ventricular ectopy (Table 4).

**DISCUSSION**

In this study, traditional and novel electrocardiographic conduction and repolarization markers of augmented arrhythmogenesis were evaluated and compared between Boxers and dogs of other breeds. In these retrospective analyses, both Boxers who had history of syncope (n=9) and those without (n=88) were included, as well as Boxers considered normal (n=12) or likely affected by ARVC (n=15) according to Holter criteria. None of the dogs had received antiarrhythmic therapy at the time the electrocardiogram was recorded. The body weight and age were considered similar between BG and NBG, although only animals ≥ 4 years old and >20kg were included in the study to minimize the impact of the dog’s size and age on electrocardiographic parameters.

**Table 1. Summary of electrocardiographic markers evaluated in this study, which are based on either myocardial conduction or repolarization**

| Classification of risk marker | Electrocardiographic marker | Definition | Pre-clinical marker correlate | Reference |
|-----------------------------|----------------------------|------------|--------------------------------|-----------|
| Conduction                  | $QRS_d$                    | QRS duration, interval between the beginning and the end of QRS complex measured in leads II, rV2 and V4 | Conduction velocity (CV) | Kurl et al. 2012 |
|                             | $QRS_D$                    | QRS dispersion, maximum difference between QRS durations measured in the right (rV2) and left (V4) precordial leads | CV difference between two regions | Tse et al. 2015 |
| Repolarization              | $QT_c$                     | QT interval at DII corrected for heart rate using the Van de Water' formulae | Action potential duration (APD) | Surawicz 1987 |
|                             | $QT_D$                     | Maximum difference between QT intervals in two leads of the 10-lead ECG (applying the correction proposed by Malik & Batchvarov 2000) | Difference in APD values between two regions | Linker et al. 1992 |
|                             | $T_{peak-T_{end}}$         | Interval from the peak to the end of the T-wave, measured in leads II, rV2 and V4 | Dispersion of late repolarization | Xia et al. 2005a |
|                             | $T_{peak-T_{end}}/QT_c$    | Interval from the peak to the end of the T-wave divided by QTc | Dispersion of repolarization divided by APD | Castro Hevia et al. 2006 |
|                             | $JT_{peak}/JT$             | $JT_{peak}$ interval from J-point to peak of the T-wave divided by JT interval | Dispersion of repolarization normalized to JT interval | Alvarado-Serrano et al. 2003, Brisinda et al. 2004 |
|                             | $T_{peak-T_{end}}/JT_{peak}$ | Measured in leads II, rV2 and V4 | Dispersion of repolarization normalized to $JT_{peak}$ interval | Alvarado-Serrano et al. 2003, Brisinda et al. 2004 |
The pathological features of ARVC in both people and Boxer dogs, which are considered as a spontaneous animal model for the study of the human ARVC, include cardiomyocyte atrophy and fibrofatty replacement (Marcus et al. 1982, Basso et al. 2015). Depolarization delay in right precordial leads is a common feature in people with ARVC (Nasir et al. 2004, Cox et al. 2008). Thus, the QRS prolongation (>110ms) in right precordial leads is considered a major criteria for diagnosis of ARVC in people (Marcus et al. 2010), and an independent predictor of risk of sudden cardiac death in the general population (Kurl et al. 2012).

However, our findings suggest that the electrocardiographic surrogates of conduction velocity of myocardial depolarization impulse behave similarly in Boxers and in medium to large non-Boxer dogs, and Boxers with a high degree of ventricular ectopy (>300 VPCs/24h) compared to those with a low number of VPCs (0-20 VPCs/24h).

The QT interval reflects the duration of the action potential at the cellular level, being associated with depolarization and triggered activity. The QT interval in people with type 1 diabetes is considered an independent predictor of cardiovascular mortality (Stettler et al. 2007). However, although it is a poor indicator of heterogeneity in repolarization across the heart, it is known that increased heterogeneities in repolarization increase the risk of arrhythmias (Tse & Yan 2016). No

Table 2. Comparison of electrocardiographic surrogates of myocardial conduction and repolarization in Boxer dogs (n=97) and non-Boxer dogs (n=103) obtained from the 10-lead standard electrocardiography

| Electrocardiographic marker | Boxer  | non-Boxer | P    | Pre-clinical marker correlate                  |
|-----------------------------|--------|-----------|------|-----------------------------------------------|
| QRS lead II                 | 67 (61-76) ms | 60 (57-67) ms | 0.06 | Conduction velocity (CV)                      |
| QRS lead rV2                | 70 (67-77) ms | 67 (60-73) ms | 0.11 |                                               |
| QRS lead V4                 | 64 ± 9 ms | 64 ± 10 ms | 0.89 |                                               |
| QRS D                       | 10 (3-16) ms | 7 (3-13) ms | 0.50 | CV difference between two regions              |
| QTc                         | 257 (246-272) ms | 254 (242-258) ms | 0.22 | Action potential duration (APD)               |
| QTc                         | 7 (5-11) ms | 7 (5-8) ms | 0.54 | Difference in APD values between two regions   |
| T_peak lead II              | 34 ± 9 ms | 31 ± 7 ms | 0.22 | Dispersion of late repolarization             |
| T_peak lead rV2             | 45 ± 8 ms | 38 ± 10 ms | 0.01*|                                               |
| T_peak lead V4              | 35 ± 9 ms | 34 ± 12 ms | 0.51 |                                               |
| T_peak lead II / QTc lead II| 0.14 ± 0.04 | 0.12 ± 0.03 | 0.34 | Dispersion of repolarization divided by APD   |
| T_peak lead rV2 / QTc lead rV2| 0.17 (0.15-0.19) | 0.15 (0.13-0.18) | 0.07 |                                               |
| T_peak lead V4 / QTc lead V4| 0.13 (0.11-0.16) | 0.12 (0.09-0.17) | 0.67 |                                               |
| JT DII                      | 146 ± 22 ms | 150 ± 10 ms | 0.47 | Global dispersion of repolarization           |
| JT rV2                      | 150 ± 19 ms | 148 ± 8 ms | 0.77 |                                               |
| JT V4                       | 153 ± 20 ms | 151 ± 12 ms | 0.74 |                                               |
| JT peak DII                 | 112 ± 25 ms | 121 ± 11 ms | 0.21 | Dispersion of early repolarization            |
| JT peak rV2                 | 105 ± 18 ms | 110 ± 7 ms | 0.29 |                                               |
| JT peak V4                  | 119 ± 20 ms | 117 ± 14 ms | 0.78 |                                               |
| JT peak JT lead II          | 0.76 (0.71-0.83) | 0.82 (0.76-0.86) | 0.08 | Dispersion of repolarization normalized to JT interval |
| JT peak JT lead rV2         | 0.72 (0.67-0.75) | 0.73 (0.71-0.79) | 0.04*|                                               |
| JT peak JT lead V4          | 0.78 (0.73-0.81) | 0.77 (0.73-0.83) | 0.64 |                                               |
| T_peak lead II / JT peak lead II| 0.33 (0.23-0.42) | 0.26 (0.19-0.29) | 0.08 | Dispersion of repolarization normalized to JT peak interval |
| T_peak lead rV2 / JT peak lead rV2| 0.41 (0.35-0.51) | 0.37 (0.27-0.40) | 0.03*|                                               |
| T_peak lead V4 / JT peak lead V4| 0.29 (0.25-0.37) | 0.27 (0.18-0.40) | 0.50 |                                               |

* Statistical significance (P<0.05).

Table 2. Comparison of electrocardiographic surrogates of myocardial conduction and repolarization in Boxer dogs (n=97) and non-Boxer dogs (n=103) obtained from the 10-lead standard electrocardiography

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Fig.2. Box-plots of data distribution for electrocardiographic markers of repolarization found to differ between Boxer (n=97) and non-Boxer (n=103) dogs.
differences were noticed either in QTc or QTd between groups in this investigation.

The fibrofatty tissue that replaces healthy myocardium in ARVC is thought to contribute to the development of ventricular arrhythmias by slowing intra-ventricular conduction, and acting as a substrate for arrhythmias through a scar-related macro-re-entry mechanism (Fontaine et al. 1984). The Tpeak–Tend interval is important as a lead-dependent marker of global dispersion of late repolarization (Xia et al. 2005a, 2005b), since repolarization dispersion varies in different cardiac regions (Bieganowska et al. 2013). Therefore, it was proposed that Tpeak–Tend interval should be determined from right precordial leads for right ventricular disorders (Tse & Yan 2016). When the right precordial lead rV2 is considered, our results for the electrocardiographic markers Tpeak–Tend and Tpeak–Tend/JTpeak suggest that the late dispersion of RV repolarization occurs more slowly in Boxers than in other breeds. In people Tpeak–Tend is increased in short QT syndrome (Watanabe et al., 2010), Brugada syndrome (Zumhagen et al. 2016), and patients with "torsade des points" (Yamaguchi et al. 2003).

While Tpeak–Tend represents late repolarization, JTend represents early repolarization (Johannesen et al. 2014a, 2014b), and both are potential markers of abnormal repolarization (Clemente et al. 2012). In people, the JTend/JT and the Tpeak–Tend/JTpeak showed a higher sensitivity and specificity than Tpeak–Tend/JT for identifying patients who suffered myocardial infarction (Alvarado-Serrano et al. 2006). The dispersion of repolarization normalized to JT or JTpeak interval at rV2 differs in Boxers form non-Boxers in our study. Unexpectedly, the marker JTpeak/JT was slightly lower in BG, mainly due to the interquartile range difference between groups, since median values were similar in both groups.

The small and unequal sample size between syncopal and non-syncopal Boxers may have contributed significantly to our findings in such a comparison. According to our results, myocardial conduction and repolarization is similar in supposedly healthy and syncopal Boxers. As previously mentioned, a diagnosis of ARVC in veterinary patients is based on a combination of findings, including ventricular arrhythmias, syncope, and familial history of ARVC. Many disorders, such as neurocardiogenic bradyarrhythmia (Thomason et al. 2008), can ultimately lead to syncopal events. Antiarrhythmic drugs such as sotalol and mexiletine act by blocking ion channels, potassium and sodium respectively, in the cellular membrane, thus, interfering in electrocardiographic measurements, especially those related to conduction and repolarization. Since most syncopal Boxers admitted to a referring cardiology service are already receiving antiarrhythmic therapy, it is challenging to study electrocardiographic markers in such individuals.

The results of this study should be interpreted in the context of its limitations. This was a retrospective investigation and accepts the inherent criticisms of the methodology. Moreover, it is difficult to determine the end of the T-wave on conventional electrocardiography, as previously reported by many researchers and this may introduce inaccuracies (Bieganowska et al. 2013, Kaplan et al. 2015, Tse & Yan 2016, Zumhagen et al. 2016). Also, the low number of syncopal Boxers, and those with a 24-hour Holter recording may have compromised the accuracy of our analysis.

**CONCLUSIONS**

Myocardial electrical conduction occurs similarly in Boxer dogs and non-Boxer dogs.

Global dispersion of myocardial late repolarization in the right precordial lead rV2 occurs more slowly in Boxers than dogs from other breeds.

### Table 3. Comparison of electrocardiographic surrogates of myocardial conduction and repolarization in syncopal (n=9) and non-syncopal Boxer dogs (n=88) obtained from 10-lead standard electrocardiography

| Electrocardiographic marker | Non-syncopal (n=88) | Syncopal (n=9) | p |
|-----------------------------|---------------------|---------------|---|
| QRSd lead II                | 63 (60-70) ms       | 73 (63-80) ms | 0.11 |
| QRSd lead rV2               | 67 (63-73) ms       | 73 (67-80) ms | 0.14 |
| QRSd lead V4                | 64 ± 8 ms           | 63 ± 8 ms     | 0.60 |
| QRS0                        | 6 (3-13) ms         | 10 (6-17) ms  | 0.21 |
| QTd                         | 257 ± 16 ms         | 267 ± 28 ms   | 0.19 |
| QTd (4-10) ms               | 5 (7-11) ms         | 5 (7-11) ms   | 0.26 |
| Tpeak–Tend lead II          | 31 ± 10 ms          | 35 ± 9 ms     | 0.26 |
| Tpeak–Tend lead rV2         | 43 (38-53) ms       | 50 (37-50) ms | 0.77 |
| Tpeak–Tend lead V4          | 37 ± 11 ms          | 33 ± 9 ms     | 0.34 |
| Tpeak–Tend/QT lead II       | 0.12 ± 0.04         | 0.13 ± 0.04   | 0.38 |
| Tpeak–Tend/QT lead rV2      | 0.16 (0.15-0.20)    | 0.18 (0.16-0.19) | 0.83 |
| Tpeak–Tend/QT lead V4       | 0.14 ± 0.05         | 0.12 ± 0.05   | 0.13 |
| JTpeak/JT lead II           | 0.79 (0.73-0.85)    | 0.75 (0.73-0.82) | 0.24 |
| JTpeak/JT lead rV2          | 0.72 (0.70-0.75)    | 0.71 (0.65-0.73) | 0.14 |
| JTpeak/JT lead V4           | 0.77 ± 0.06         | 0.78 ± 0.07   | 0.52 |
| Tpeak–Tend/JTpeak lead II   | 0.26 (0.20-0.36)    | 0.34 (0.24-0.40) | 0.21 |
| Tpeak–Tend/JTpeak lead rV2  | 0.38 (0.34-0.47)    | 0.44 (0.38-0.52) | 0.50 |
| Tpeak–Tend/JTpeak lead V4   | 0.29 (0.25-0.37)    | 0.28 (0.20-0.34) | 0.57 |

### Table 4. Comparison of electrocardiographic surrogates of myocardial conduction and repolarization obtained from 10-lead standard electrocardiography in Boxer dogs considered normal (n=12) and affected by ARVC (n=15) according to the degree of ventricular ectopy on 24-hour Holter monitoring

| Electrocardiographic marker | Normal Boxers (n=12) | ARVC Boxers (n=15) | P |
|-----------------------------|----------------------|--------------------|---|
| QRSd lead II                | 63 (60-67) ms        | 73 (63-80) ms      | 0.05 |
| QRSd lead rV2               | 69 ± 7 ms            | 72 ± 7 ms          | 0.15 |
| QRSd lead V4                | 67 (60-70) ms        | 63 (57-70) ms      | 0.48 |
| QRS0                        | 8 ± 9 ms             | 9 ± 6 ms           | 0.37 |
| QTd                         | 260 ± 15 ms          | 267 ± 28 ms        | 0.40 |
| QTd (4-11) ms               | 5 (7-11) ms          | 7 (5-11) ms        | 0.25 |
| Tpeak–Tend lead II          | 32 ± 10 ms           | 35 ± 9 ms          | 0.33 |
| Tpeak–Tend lead rV2         | 43 (37-54) ms        | 50 (37-50) ms      | 0.99 |
| Tpeak–Tend lead V4          | 39 ± 12 ms           | 33 ± 9 ms          | 0.14 |
| Tpeak–Tend/QT lead II       | 0.13 ± 0.04          | 0.13 ± 0.04        | 0.45 |
| Tpeak–Tend/QT lead rV2      | 0.16 (0.15-0.19)     | 0.18 (0.16-0.19)   | 0.79 |
| Tpeak–Tend/QT lead V4       | 0.15 ± 0.05          | 0.12 ± 0.05        | 0.07 |
| JTpeak/JT lead II           | 0.78 (0.72-0.87)     | 0.75 (0.73-0.82)   | 0.38 |
| JTpeak/JT lead rV2          | 0.73 (0.69-0.75)     | 0.71 (0.65-0.73)   | 0.21 |
| JTpeak/JT lead V4           | 0.76 ± 0.07          | 0.79 ± 0.06        | 0.36 |
| Tpeak–Tend/JTpeak lead II   | 0.24 (0.19-0.37)     | 0.34 (0.24-0.40)   | 0.23 |
| Tpeak–Tend/JTpeak lead rV2  | 0.43 ± 0.15          | 0.45 ± 0.10        | 0.30 |
| Tpeak–Tend/JTpeak lead V4   | 0.34 ± 0.15          | 0.29 ± 0.11        | 0.27 |
Traditional and novel electrocardiographic markers of myocardial conduction and repolarization were obtained in Boxers and non-Boxers dogs >20kg.

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