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Cardiomyopathy in Boxer dogs: A retrospective study of the clinical presentation, diagnostic findings and survival

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Abstract *Objectives:* To retrospectively compare and contrast the clinical presentation, diagnostic findings and survival in Boxer dogs with cardiomyopathy, with or without left ventricular (LV) systolic failure.
Animals, materials and methods: Medical records of Boxers referred between 1993 and 2008 in which a diagnosis of ventricular arrhythmias and/or cardiomyopathy was made, were reviewed. Dogs were divided into two groups according to their left ventricular (LV) systolic diameter, group A normal (20 dogs) or group B dilated (59 dogs).
Results: Dogs in group A had a better outcome than dogs in group B (median survival time of 124 and 17 weeks respectively, $p < 0.001$). In group B, dogs with a history of collapse had a worse outcome (median survival time of 10 weeks) compared with dogs not showing collapse (median survival time 24 weeks) ($p = 0.031$).
Conclusions: The majority of dogs, in this UK study, presented with the myocardial dysfunction form of the disease, with LV dilation and congestive heart failure signs. The prognosis was worse in dogs with LV dilation compared to dogs with a normal LV and ventricular arrhythmias. In the Boxers with LV dilation, dogs with collapse had a worse prognosis than those without.

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Introduction

Harpster first described "Boxer cardiomyopathy" (BCM) in 1983 proposing three clinical categories of the disease: concealed, overt and a myocardial dysfunction form.[1] The concealed form is characterized by the absence of clinical signs but presence of ventricular premature complexes (VPCs). In the overt form, syncope or episodic weakness and tachyarrhythmias are present, while the third group is characterized by myocardial systolic dysfunction (affecting mainly the left ventricle) sometimes with congestive heart failure (CHF) and arrhythmias.[1–3]

Boxer cardiomyopathy has been characterized as a degenerative myocardial disease with extensive and unique right ventricular histologic findings that include myocyte atrophy and fatty infiltration.[1] Similarities in clinical presentation, pathological findings and presumed aetiology with a human myocardial disease called arrhythmogenic right ventricular cardiomyopathy, have suggested reclassification of the disease as Boxer arrhythmogenic right ventricular cardiomyopathy (ARVC).[3,4]

In Boxers, ARVC is an adult-onset familial disease apparently inherited as an autosomal dominant trait.[5] ARVC is primarily an electrical disease sometimes associated with myocardial dysfunction. Diagnosis is best based on a combination of findings that may include a family history of disease, a history of syncope, presence of ventricular tachyarrhythmias with a left bundle branch block (LBBB) morphology or post mortem findings. Most affected dogs have a normal echocardiographic examination, particularly with regard to evaluation of the size and function of the left ventricle.[3]

Idiopathic dilated cardiomyopathy (DCM) is a primary myocardial disorder characterized by reduced contractility and ventricular dilation involving the left ventricle or both ventricles, of unknown or uncertain aetiology.[6,7] Some Boxer dogs have a clinical and echocardiographic presentation consistent with idiopathic dilated cardiomyopathy, of which the etiology is unknown. Harpster refers to these cases as the myocardial dysfunction form (category 3) which is considered to be less common.[3]

Whether the three forms proposed by Harpster represent a continuum of the disease has not been well documented and it is also not clear how many, if any, cases of cardiomyopathy in Boxers are due to "conventional" idiopathic DCM or other forms of myocardial disease.

Much research has been carried out to try to identify a mutation or genetic abnormality linked to ARVC. In cardiomyopathic Boxer dogs myocardial calstabin2 mRNA and protein were significantly decreased as compared to healthy control dogs[8] and recently a 7 base pair deletion in a regulatory region of a calcium modulating gene was identified and observed to be highly associated with the disease status.[9]

There are few publications describing populations of Boxers affected by cardiomyopathy and the majority were reported by Harpster in 1983 and 1991.[1,2] Moreover, most of the more recent work on ARVC comes from the USA[9–17] and no survival studies are available.

The aim of this study was to retrospectively evaluate signalment, clinical and diagnostic findings, survival and prognostic factors in a population of Boxer dogs with cardiomyopathy from the UK, in order to improve our knowledge of this disease. Given the difficulties in differentiating ARVC from idiopathic DCM affected Boxers were divided into two groups according to their left ventricular systolic diameter, either normal or increased. The two groups were then compared in terms of presentation, outcome and possible relationship between the two populations.

Materials and methods

Medical records of client-owned Boxer dogs referred to the Veterinary Cardiorespiratory Centre, Kenilworth, UK, between January 1993 and July 2008, in which a diagnosis of cardiomyopathy or ventricular arrhythmia had been made, were reviewed. Only dogs that were referred with a clinical history or presence of a clinical or ECG abnormality were included in the study. Dogs examined for routine breed screening were excluded. Information obtained included: age, sex, clinical presentation; results of standard 6-lead electrocardiography (HR, rhythm, presence and morphology of VPCs), 24-h Holter monitoring, thoracic radiography, Doppler echocardiography and survival time.

Diagnosis of cardiomyopathy was based on a combination of factors including a history of syncope or exercise intolerance, presence of ECG and/or Holter abnormalities (number and complexity of VPCs) and echocardiographic examination.[3] Dogs in which an ECG was not performed, but that underwent a Holter study, as well as dogs in which ECG was performed by the primary veterinarian and returned (thus not

available for our retrospective analysis, but the findings were present in the medical record) were included. We used a modification of the Holter ventricular arrhythmia classification grading defined by Meurs[3] including arrhythmias present on both ECG and Holter as detailed in Table 1. Dogs were excluded if there was gross left atrial dilation (i.e. significantly larger than the diameter of the left ventricle in diastole) that could suggest primary mitral valve disease.[6] Dogs with aortic velocity $>$ 2.4 m/s, with congenital or other acquired heart diseases, myocardial failure secondary to rapid supraventricular tachycardia (where myocardial function returned to normal after the arrhythmia was controlled), or systemic diseases that might affect the cardiovascular system (e.g. hypothyroidism) were excluded.

Doppler echocardiographic examinations were performed according to standard criteria for dogs[18] (with continuous ECG monitoring). Left ventricular measurements were compared to normal values for the Boxer dog[19] and for the purposes of this study, dogs were divided into two groups based on echocardiographic measurement (M-mode and 2-D) of the systolic left ventricular diameter. When M-mode and 2-D measurements were different, the larger value was used. Group A: dogs with a systolic LV internal diameter $<$ 35 mm were defined as normal and group B: dogs with systolic LV internal diameter $>$ 35 mm were defined as dilated. Additionally, to compare the usefulness of the cut-off chosen in this study, left ventricular measurements were evaluated using an allometric scale[20] and the echocardiographic ratio indices (ERIs).[21]

Left atrial (LA) measurements in both long and short axis views were recorded and compared to published normal values.[22] Right ventricular chamber size was subjectively assessed by comparison with the left ventricle in the right parasternal long-axis view and left apical view.

Table 1 ECG and Holter arrhythmia classification.

ECG class 1	Single VPCs
ECG class 2	Couplets/triplets
ECG class 3	VT
Holter class 1	$<$1000 single VPCs/24 h
Holter class 2	$>$1000 single VPCs/24 h
Holter class 3	$<$1000 VPCs/24 h, couplets, triplets, VT
Holter class 4	$>$1000 VPCs/24 h, couplets, triplets, VT

VPCs, ventricular premature complexes; VT, ventricular tachycardia.

Right ventricular dilation was defined as follows: mild dilation if it was between 30 and 50% of left ventricular size, moderate dilation if it was from 50 to 100% of left ventricular size, and severe dilation when right ventricular size exceeded that of the left ventricle. Assessment of cardiomegaly on thoracic radiography was based on the vertebral heart scale system (VHS)[23] and clinical experience, and the presence of signs of congestive heart failure (pulmonary venous congestion or pulmonary oedema) was recorded.

Date and cause of death (either spontaneous death or euthanasia) were recorded and survival time was measured from the date of referral. Dogs euthanized for severe chronic heart failure were considered as cardiac-related deaths. Sudden deaths were counted as cardiac-related if no other cause of death was obvious. Dogs still alive, dogs that died or were euthanized for reasons unrelated to cardiac disease were censored in the statistical analysis; subjects lost to follow-up were included in the survival analysis up until the last time point at which they were known to be alive and then were thereafter censored in the analysis.

Statistical analysis

Continuous variables were assessed for significant differences between the groups. The Shapiro–Wilk test was used to verify variables' normal distribution. If the distribution was normal, a *t*-test was used to compare the means of two continuous variables; the Mann–Whitney *U* test was used with non-normally distributed variables. The Kaplan–Meier method was used to estimate survival function and plot time to event curves. After accepting the assumption of proportional hazards, multivariate Cox proportional hazards analysis was performed to determine whether any variable was associated with survival time, in each group separately first, then in the whole sample. Variables assessed for their effect on outcome in the whole sample were: group, presence of ventricular arrhythmias (considering both ECG trace and Holter study), ECG class, presence of ventricular tachycardia (VT) (considering both ECG and Holter study) and collapse. ECG class and collapse were assessed in group A; presence of ventricular arrhythmias, presence of VT, ECG class, and collapse were assessed in group B. Hazard ratio (HzR) and 95% confidence intervals (CI) were calculated. A Pearson's chi-square test was used to assess a significant association between the presence of ventricular arrhythmias and syncope or the presence of VT and syncope.

A *P*-value <0.05 was considered significant. Basic descriptive statistical analyses were performed using Microsoft Excel, Cox proportional hazard and survival analyses were performed with a commercially available software program (SPSS version 17).

Results

A total of 79 dogs met the inclusion criteria for the study; there were 20 in group A and 59 in group B. Males were overrepresented with a M:F ratio of 1.9: 1 in group A and 1.4: 1 in group B. Mean (±SD) age at presentation was 91.7 months (±32.2) (range 20—122) in group A and 68.6 months (±28.6) (range 8—120) in group B; age distribution is shown in Fig. 1 and Table 2.

The median (interquartile range) duration of clinical signs prior to referral was 2 weeks (1—3.25; range 0—72) in group A and 4 weeks (2—8; range 1—104) in group B. Two dogs in group B had a long duration of clinical signs before referral; the reported signs were collapse, exercise intolerance and weakness. Although these signs can be reported in dogs with congestive heart failure, considering their long duration, they are probably more typical of category 2 ARVC.

The most common presenting clinical sign in both groups was collapse (80% and 67.7% in group A and B respectively); cough, breathlessness and exercise intolerance were more common in group B dogs. On clinical examination a systolic murmur was present in 6/20 patients in group A (grade I/VI in 4 dogs, grade II in 1 dog, grade III in 1 dog) and in 22/59 dogs in group B (grade I in 12 dogs, grade II in 6 dogs, grade III in 3 dogs, grade IV in 1 dog). Pallor of the mucous membranes and a weak pulse were noted in dogs of both groups, while gallop rhythm and ascites were present only in group B dogs. The presence of an arrhythmia on clinical examination was not recorded in the clinical records in the majority of dogs, but was detected on ECG and/or Holter recording; it is impossible to know the real prevalence of this clinical finding, therefore we decided not to evaluate this. Signalment, clinical signs and physical examination findings for all dogs are displayed in Table 2.

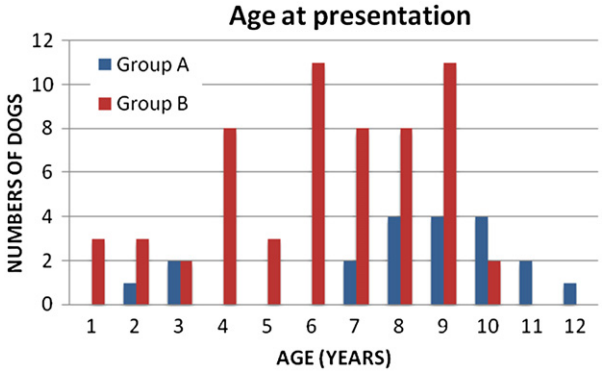

Figure 1 Distribution of age at presentation (years) for group A and B dogs.

Electrocardiograms were available for review in 18/20 and 57/59 dogs in group A and B respectively. Mean (SD) heart rate was 133.5 (26.8) bpm in group A and 171.6 (45.6) bpm in group B. In both groups VPCs were the most commonly recorded arrhythmia, mainly present as single VPCs (ECG class 1), but the prevalence was higher in group A. In group B, supraventricular premature complexes (SVPCs) and atrial fibrillation (AF) were also present (Fig. 2). Holter monitoring was performed in 10 dogs in group A and 7 in group B. In 6 dogs of group A which underwent both a standard ECG and Holter recording, the ECG tracing was graded as class 1 (single VPCs) whereas the Holter showed a high number of VPCs with increased complexity and periods of ventricular tachycardia (Holter class 2 in 1 dog, class 3 in 1 dog, class 4 in 4 dogs). In group B, in 3 cases Holter monitoring demonstrated the presence of VT, not evident on ECG and in 2 dogs where the ECG was normal, VPCs were demonstrated by Holter. ECG and Holter findings for both groups are displayed in Table 3. Morphology of VPCs seen on a lead II ECG or on Holter was consistent with LBBB morphology in the majority of patients in both groups and right bundle branch morphology (RBBB) was more frequent in group B dogs (Fig. 3).

Thoracic radiographs were performed in 12 dogs in group A and 51 dogs in group B and revealed the presence of cardiomegaly in 82.3% of dogs in group B, associated with signs of pulmonary oedema in 58.8%; in group A, 1 dog showed cardiomegaly.

Echocardiographic examination revealed mild/moderate right ventricular (RV) enlargement, mitral and/or tricuspid regurgitation in a small percentage of boxers in group A (mild/moderate RV enlargement in 10% and 5% respectively, mitral regurgitation in 5% and tricuspid regurgitation or both in 10%). In group B concurrent RV dilation was uncommon and mitral and tricuspid insufficiency were common (mitral regurgitation in 38.9% and both mitral and tricuspid regurgitation in 40.6%). Mean LVDs (SD) was 29.7 (4.1) and 48 (6.6) mm respectively for group A and group B dogs. The Cornell index for the LVIDs was in the normal range (0.71—1.26)[20] in all the dogs in group A and group B dogs had values outside this range. Using the ERIs proposed for the Boxer breed, all the dogs in group

Table 2 Signalment in the whole population and groups; presenting signs and clinical examination findings in groups A and B.

	Whole population	Group A (LVDs <35 mm)	Group B (LVDs >35 mm)
Number of dogs	79	20	59
Male	60.7%	65%	59.3%
Female	39.3%	35%	40.6%
Ratio M:F	1.5:1	1.9:1	1.4:1
BW (Kg) mean ± SD	30.3 ± 4.7	32.5 ± 3.7	29.7 ± 4.6
Age (months) mean ± SD	74.5 ± 31.1	91.7 ± 32.2	68.6 ± 28.6
Clinical findings			
Cough		15%	64.4%
Breathlessness		30%	55.9%
Exercise intolerance		20%	55.9%
Collapse		80%	67.7%
Weakness		30%	38.9%
Lethargy		0	15.2%
Poor appetite		5%	28.8%
Weight loss		5%	30.5%
Murmur		30%	37.2%
Gallop sounds		0	11.4%
Weak pulse		10%	30.5%
Pallor		25%	15.2%
Ascites		0	16.9%

A presented a weight-based LVIDs (WLVIDs) in the proposed normal range (0.68—1.35),[21] while all the dogs in group B had a WLVIDs out of the normal range. Echocardiographic findings are displayed in Table 4.

Three dogs were still alive at the end of the study and 8 dogs were lost to follow-up. Sixty-three dogs died or were euthanized for cardiac reasons (11 in group A, 52 in group B) and 5 dogs died or were euthanized for reasons unrelated to cardiomyopathy (leukemia, mammary neoplasia, epilepsy (2 dogs), heart-base neoplasia) (4 in group A and 1 in group B). A total of 75 dogs were available for survival analysis.

As expected because of the division into groups based on LV diameter, groups differed significantly for all other echocardiographic parameters: left ventricular diameter in diastole (LVDd), fractional shortening (FS%), LA diameter in long-axis view, LA diameter in short axis view ($P < 0.001$). Furthermore age ($P = 0.002$) and heart rate ($P < 0.001$) were significantly different between groups.

Comparing survival times, dogs in group A had a better outcome than dogs in group B. Median survival time was 124 weeks (95% CI = 46.7—201.3) for group A dogs and 17 weeks (95% CI = 14.6—19.4) for group B dogs ($P < 0.001$) (Fig. 4). Hazard ratio of group A compared to group B was 0.207 (95% CI = 0.103—0.418). Other variables ECG class ($P = 0.36$), ventricular arrhythmias ($P = 0.48$), VT ($P = 0.36$), collapse ($P = 0.47$) did not have a significant effect on the risk of cardiac-related death. No significant association was found between the presence of VPCs and syncope ($P = 0.07$) or presence of VT and syncope

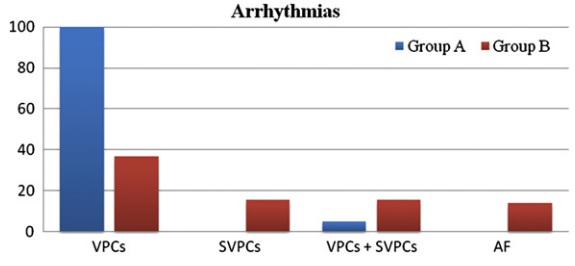

Figure 2 Prevalence of arrhythmias (%) in dogs of group A and B. VPCs, ventricular premature complexes; SVPCs, supraventricular premature complexes; AF, atrial fibrillation.

Table 3 ECG and Holter findings in groups A and B.

	Group A	Group B
Mean HR (bpm)	133.5 ± 26.8	171.6 ± 45.6
ECG class 1	72.2%	51.6%
ECG class 2	0	22.6%
ECG class 3	27.8%	25.8%
Holter class 1	2/10	1/7
Holter class 2	1/10	1/7
Holter class 3	1/10	2/7
Holter class 4	6/10	3/7

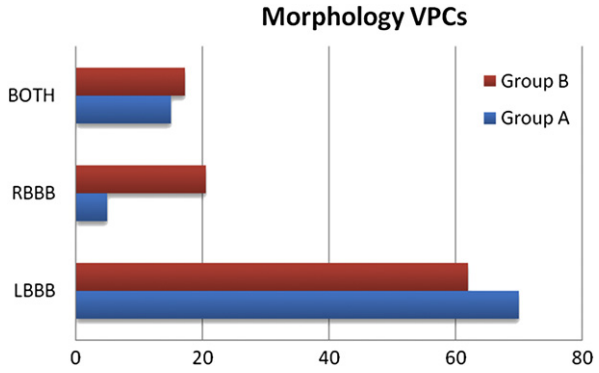

Figure 3 Morphology of VPCs on ECG/Holter in dogs of group A and B. LBBB, left bundle branch block; RBBB, right bundle branch block.

($P = 0.29$). In group A no variable was significantly associated with survival when considering cardiac-related deaths (ECG class $P = 0.21$, collapse $P = 0.86$). In group B dogs the only variable that was significantly associated with outcome was the presence of collapse ($P = 0.031$); dogs in which a history of collapse was present had a worse outcome with a median survival time of 10 weeks (95% CI = 0—21.3) compared with dogs not showing collapse (median survival time 24 weeks, 95% CI = 15.5—32.5) (Fig. 5). Hazard ratio of dogs with a history of collapse was 1.931 (95% CI = 1.060—3.521). Other variables ECG class ($P = 0.09$), presence of ventricular arrhythmias ($P = 0.17$), presence of VT ($P = 0.058$) were not significant, although VT was close to the chosen 5% level of significance.

Table 4 Echocardiographic findings in groups A and B.

	Group A	Group B
LVDd (mm) mean ± SD	39.1 ± 5.1	54.2 ± 6.9
LVDs (mm) mean ± SD	29.7 ± 4.1	48 ± 6.6
FS (%)mean ± SD	25.8 ± 7.4	11.8 ± 5.4
LA long-axis (mm) mean ± SD	39.8 ± 5.4	54.7 ± 6.9
LA short axis (mm) mean ± SD	35.8 ± 9.3	48.9 ± 7.7
Mild RV dilation	10%	15.2%
Moderate RV dilation	5%	8.4%
MR only	5%	38.9%
TR only	10%	0
MR + TR	10%	40.6%

LVDd, left ventricular diameter diastole; LVDs, left ventricular diameter systole; FS, fraction shortening; LA, left atrium; RV, right ventricle; MR, mitral regurgitation; TR, tricuspid regurgitation.

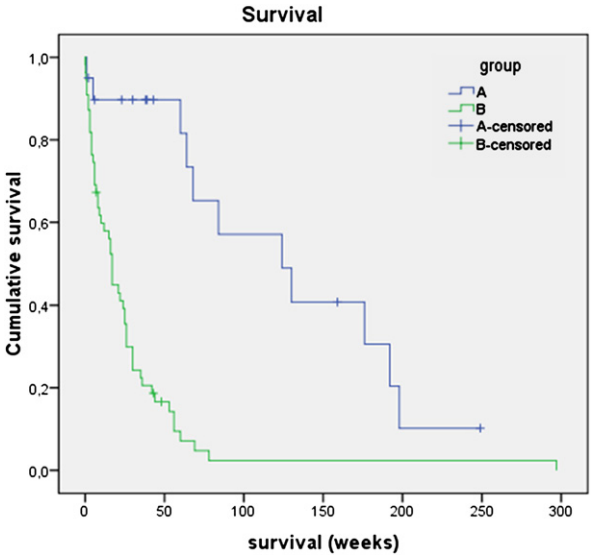

Figure 4 Kaplan—Meier survival curve in the overall population of dogs (group A and B). Dogs in group A (normal left ventricle) had a median survival time of 124 weeks (95% CI = 46.7—201.3), dogs in group B (dilated left ventricle) had a median survival time of 17 weeks (95% CI = 14.6—19.4) ($P < 0.0001$).

Discussion

Boxer cardiomyopathy in the UK has close similarities to the disease in the USA, but there seems to be a different prevalence of the three Harpster's categories in the 2 countries. Meurs reported

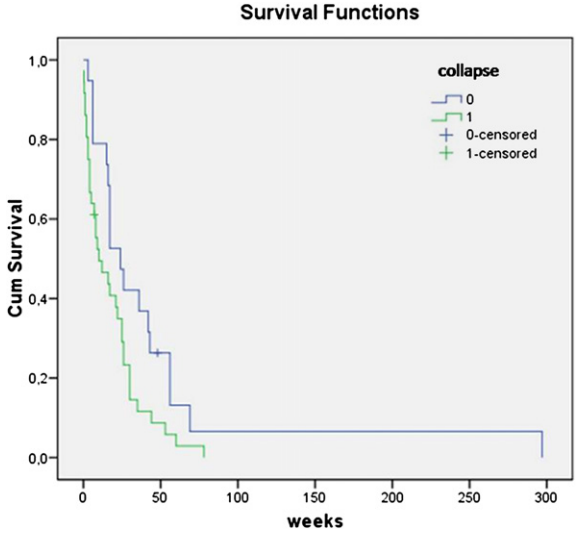

Figure 5 Kaplan—Meier survival curve in group B dogs. Dogs in which collapse was present (1) had a median survival time of 10 weeks (95% CI = 0—21.3), dogs without collapse (0) had a median survival time of 24 weeks (95% CI = 15.5—32.5) ($P = 0.031$).

that only a small percentage of adult Boxers with tachyarrhythmias are observed to have LV dilation with systolic dysfunction[3] and Harpster reported an almost equal distribution of dogs in his 3 categories.[1,2] Our work showed a different distribution of dogs, with most of the dogs having the myocardial dysfunction form with LV dilation and signs of CHF. As suggested by Wotton this could be due to a different prevalence of the "DCM type" in the UK and USA; BCM in the UK may be less genetically widespread in the breed than in the USA, appearing to be effectively restricted to three family lines (all with American ancestry) with an autosomal dominant pattern of inheritance.[24]

The signalment for the dogs in this study was similar to that reported in previous publications. For all dogs, males were more commonly affected than females which is similar to Harpster's findings.[1,2] In both groups A and B, males were overrepresented. The difference between males and females in group B was not as marked as in group A, in partial agreement with previous studies of Boxers with LV dysfunction which reported a gender ratio of 50:50 M:F[25] and 45:55 M:F.[15] In group A, a male predominance was evident, suggesting a predisposition in males to ventricular arrhythmias or lesser likelihood of males progressing to CHF. Mean age at presentation in the whole population and in the subgroups was similar to that reported by Harpster,[1,2] by Basso et al.[4] in Boxers with arrhythmias and by Baumwart et al.[15] in Boxers with LV dysfunction. Mean age differed significantly between group A and group B dogs, with group A dogs being older than group B. Therefore it would seem difficult to believe from this result that group B dogs represent an advanced, and thus subsequent, stage of the disease.

The main difference in the presenting clinical signs in the 2 groups was the presence of CHF signs in group B, but not in group A. Group B dogs were consistent with Harpster class 3 dogs[1] and Boxers with LV systolic dysfunction described by Baumwart.[15] Mean heart rate was significantly higher in group B than group A dogs, which would be consistent with signs of heart failure, due to sympathetic system activation. The most common presenting sign in both groups was collapse. This is similar to the findings of Wotton[25] who reported the presence of syncope in 80% of Boxers with DCM. In contrast, other studies reported collapse at much lower rates, 34.3% and 35% respectively.[15,1] It would be reasonable to suggest that syncope in group A would be associated with ventricular arrhythmias and in this study all dogs had VPCs on ECG/Holter. One study showed that syncopal dogs had a significantly greater number of VPCs and grade of arrhythmia, but significant variability exists and other factors may be involved in the development of syncope.[26] In some Boxers, VT and bradycardia coexist,[27] and without Holter monitoring (during a collapse), the latter cannot be excluded as the cause of clinical signs. In contrast, in group B dogs, VPCs were seen at a much lower frequency. However a large number of these dogs still presented with collapse which might suggest either there were in fact more ventricular arrhythmias than was documented by ECG alone (as few subjects had undergone a Holter study). In our study collapse was significantly and negatively associated with outcome in group B dogs. In human patients affected by DCM, syncope is associated with a significantly increased risk of sudden death, regardless of the cause of the proven etiology of the syncope.[28] In Boxers, syncope has been shown to be associated with the number of VPCs per 24 h and the arrhythmia grade[26] but the predictive value of these findings has not been examined. In our work association between presence of VPCs and syncope and between presence of VT and syncope was not statistically significant and a correlation with the number and complexity of the arrhythmia was not possible because only a small percentage of the dogs in this study had 24-h Holter monitoring. However, all the dogs in which a Holter was performed had numerous VPCs per 24 h and frequent episodes of VT which might suggest that the prevalence and complexity of ventricular arrhythmias were under-estimated by standard ECG recordings alone in this group.

The cut-off value to define the normal number of VPCs in Boxers has not been clearly defined. It is unusual for mature adult dogs to have ventricular ectopy, but it has been suggested that a small number of VPCs may be normal, particularly in an older dog.[29,30] Breed variation may exist and certain breeds may have a higher number of daily VPCs. An evaluation of more than 300 adult Boxers suggested that the finding of more than 100 VPCs/24 h in an adult Boxer is strongly suggestive of a diagnosis of ARVC, particularly if there is significant complexity.[3] In our study, in more than half the cases the Holter classification was reported as class 4 (>1000 VPCs and presence of couplets, triplets and VT); this was particularly common in group A dogs. Holter recordings showed the presence of VPCs when ECG recordings had been normal and therefore provided better assessment of the frequency and complexity of the arrhythmia where ECG recordings showed only single VPCs.

This suggests that Holter monitoring provides the best assessment of the presence, overall frequency and complexity of arrhythmias and, in hindsight, should therefore have been performed in all affected dogs.

Presence of VT detected by ECG and/or Holter in dogs with myocardial dysfunction was not associated with survival in this study, although close to statistic significance level. This could be due to the relatively small number of dogs in our work and the small percentage of subjects undergoing Holter monitoring. Complex ventricular arrhythmias are associated with increased mortality and may predict sudden death in dogs affected by DCM.[31,32] In humans with chronic heart failure, VT is an independent predictor of mortality[33] and VT lasting longer than 30s may be a negative predictor in patients with ARVC.[34] In Boxer dogs in category 1 and 2, VPCs are often numerous, but often admixed with runs of VT, thus it is most likely that fast runs of VT degenerate into ventricular fibrillation leading to sudden death.[31]

The morphology of the VPCs was consistent with LBBB in the majority of dogs in both groups. In group A, LBBB morphology was predominant, whereas in group B whilst LBBB morphology was common, additionally RBBB or both morphologies were frequent. The presence of an upright VPC in lead II, III and aVF (LBBB morphology) is suggestive of ARVC. On the basis of comparative electrophysiological studies this morphology is believed to be associated with a right ventricular origin of the VPC, although a more precise localization (septal, apical, outflow tract) has not been made.[3,11] Some of the dogs in this study showed VPCs consistent with RBBB and some with both morphologies. Possible explanations are based on evidence from pace-mapping studies, where pacing from the right ventricular septum sometimes can produce a RBBB morphology; moreover the morphology of the QRS complex might be different depending on whether the initiation is from the epicardium, mid-myocardium or endocardium.[11] Particularly in dogs of group B, RBBB morphology of the VPCs was more common than in group A dogs; these subjects had LV dilation, thus ventricular ectopy arising from the LV may be possible. In ARVC in humans, when the LV is affected, ventricular arrhythmias may appear polymorphic, suggesting an origin from different cardiac regions.[35]

While ventricular arrhythmias are characteristic of the disease, supraventricular arrhythmias have also been reported.[1] AF was not seen in any dogs in group A but was seen in 13.5% of group B dogs, probably associated with atrial dilation. Similar results have been reported by others.[1,15,25] AF seems to be a less common finding in Boxer cardiomyopathy, whereas it has been reported in higher percentages (from 30% to 80%) in large-breed dogs with DCM.[36]

Left ventricular systolic diameter obtained by echocardiographic examination was the criterion for the division of dogs into the two groups. Both Cornell index[20] and ERIs calculations[21] confirmed that LVIDs was in the normal range in all dogs of group A, while it was over the proposed range in group B dogs. The latter was particularly important for the dogs with LVIDs dimension close to the cut-off chosen (i.e. 36–37 mm). For these reasons we think our proposed LVIDs cut-off (35 mm) is reasonable and allows for dogs of different body weights to be compared in this study.

Although echocardiographic information was available in only a small number of dogs in Harpster's report, he reported that all the dogs in category 3 had LVDs >35 mm and 80% had a FS $<20\%$[2] similar to our group B dogs. In more recent reports of Boxers with myocardial failure, FS ranged from 5 to 20%[23] and Baumwart reported a mean FS of 14.4% and a mean LV systolic diameter measured in M-mode of 45 mm.[15] Valvular incompetence was reported in a small number of dogs in group A, while mitral regurgitation was a common finding in group B, often in association with tricuspid regurgitation. Despite the high percentage of valvular regurgitation in group B, murmurs were reported in a relatively low percentage. Possible explanations include under-reporting in clinical notes or difficulties with auscultation of brachycephalic dogs with respiratory noise. However this might be a normal finding, as reported in studies involving other breeds of dogs with DCM.[15,37–39]

Median survival time was significantly longer in dogs in group A than in group B, indicating that once LV dysfunction and congestive heart failure are present, the prognosis is poor. The median survival time in group B was similar to survival data reported by other authors in studies of DCM in different breeds of dogs[36,37] and by Harpster for Boxers in category 3. For the latter a prognosis of 3–6 months was reported,[2] while the prognosis in categories 1 and 2 tended to be better with many of the dogs in category 1 doing well for more than 2 years, and dogs in category 2 developing CHF during the second year.[1] Considering that group A can be representative of both Harpster's categories 1 and 2, the results of this study are similar. In man with ARVC, left ventricular dysfunction was independently associated with cardiovascular mortality.[40]

The natural history of these dogs with or without therapy is unknown, although Harpster reported that 9 dogs treated with an appropriate antiarrhythmic therapy had a better prognosis.[2] Meurs compared the effects of 4 antiarrhythmic treatments, but the study did not provide information on risk of sudden death and long-term survival. Moreover a direct relationship between the number and complexity of VPCs and the risk of sudden death has not been detected[10]; thus the ability of a treatment protocol to alter this factor does not imply an impact on survival.

It is surprising that since 1983, there has not been a prospective study to follow the clinical progression and outcome of category 1 & 2 dogs described by Harpster[1] and to determine if these do progress to category 3 disease. In human ARVC several steps are recognizable, from an early clinically "concealed" phase with or without minor arrhythmias to an "overt electrical heart disorder" with severe arrhythmias and impending cardiac arrest to a final stage of "biventricular pump failure" mimicking dilated cardiomyopathy with cardiomegaly and congestive heart failure.[41] Although dogs have been hypothesized to progress from category 1—3[2] objective data supporting this hypothesis are lacking. Harpster reported that the majority of dogs in category 2 usually develop congestive heart failure after one year[1] and Baumwart reported that 4 dogs initially examined because of ventricular tachyarrhythmias later developed LV dysfunction.[15] In our study most of the dogs with LV dilation had not previously undergone cardiac evaluations because they presented when symptomatic. However, some dogs in group B did have a long duration of clinical signs (collapse, exercise intolerance, weakness) prior to referral. This might be suggestive of Harpster category 2 (overt) form, which progressed to the myocardial dysfunction form, which prompted referral. No dogs were seen to progress from category 1 or 2 to CHF but most of the dogs with a normal LV diameter lacked follow-up echocardiographic examinations. Thus, these results do not verify nor refute progression from an arrhythmia to a left ventricular dysfunction stage. The natural history of Boxer cardiomyopathy requires further study. Hopefully more objective data will be available when a genetic test for the gene mutation recently discovered[9] is developed. Other studies are needed to confirm that the same mutation is present in Boxers from Europe and will clarify if the myocardial dysfunction form is the expression of the final stage of the disease or the expression of a different mutation, or of "conventional" DCM. At present because of the absence of a perfect diagnostic test, screening asymptomatic dogs is challenging. Annual Holter monitoring is recommended in screening of breeding dogs and significant emphasis on a single Holter monitoring is discouraged.[3] Cardiac magnetic resonance imaging (MRI) is considered highly sensitive and specific for the diagnosis of ARCV in man,[42] but in affected Boxers MRI identified no degenerative fatty changes of the RV myocardium.[43] Cardiac troponin I (cTnI) appeared to be a better marker than BNP concentration for ARVC,[16,17] but its potential value as a screening test needs to be assessed.

Limitations of this study include its retrospective nature, a number of dogs were lost to follow-up in group A, non-standardization of diagnostic tests (not all patients underwent Holter monitoring), insufficient follow-up echocardiographic examination, which could have been useful in monitoring the disease progression and finally the absence of post-mortem examinations and histological evaluation, that would have been essential to confirm the diagnosis, but were often difficult to obtain because of owners' reluctance.

Conclusion

In conclusion, this study represents a population of Boxers with cardiomyopathy from the UK. The majority of dogs, presented with the myocardial dysfunction form of the disease. Males were overrepresented, the most common clinical sign was syncope and in dogs with LV dilation signs of congestive heart failure were common. Most dogs either did not have an audible murmur at auscultation or had a low grade murmur. The majority of dogs had ventricular tachyarrhythmias, particularly with LBBB morphology; AF was not a common finding and was found only in dogs with a dilated heart. All the dogs in which a Holter was performed showed various grades of ventricular arrhythmias, which were often not detected on an ECG recording. This confirms that ECG has a low sensitivity for the detection of arrhythmias in Boxer cardiomyopathy because of their intermittent nature; thus 24-h Holter monitoring provides the best assessment of presence, overall frequency and complexity of the arrhythmia and should be used as part of the diagnosis and for monitoring treatment in all forms of Boxer cardiomyopathy. The presence of the myocardial dysfunction form was associated with a worse outcome and the presence of syncope in dogs with myocardial dysfunction was associated with a poor prognosis.

Conflict of interest

None.

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