Holter monitoring in 36 dogs with myxomatous mitral valve disease.

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Holter monitoring in 36 dogs with myxomatous mitral valve disease

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Abstract

Objective  Describe the presence of arrhythmias in dogs with myxomatous mitral valve disease (MMVD) and the potential association with class of heart failure and left atrial enlargement. Compare the standard electrocardiogram (ECG) with Holter monitoring for assessing heart rate (HR).

Experimental procedure  The study group of 36 dogs weighing less than 20 kg was divided into MMVD and no clinical signs (preclinical) or MMVD and clinical signs (clinical). A standard echocardiogram, ECG and 24-h Holter recording were obtained in all dogs.

Results  Minimum and mean Holter HRs were higher in the clinical group than in the preclinical group. Clinical dogs had more ventricular arrhythmias than preclinical dogs. An enlarged left atrium was associated with the presence of more supraventricular arrhythmias.

Conclusions  Arrhythmias are a common finding in dogs with MMVD and Holter monitoring is a reliable tool for both HR monitoring and diagnosis.

Abbreviations

AF
  atrial fibrillation
APC
  atrial premature complex
ECG
Myxomatous mitral valve disease (MMVD) is the most commonly acquired valvular disease in dogs\textsuperscript{1,2} and accounts for 75–80\% of canine cardiac diseases.\textsuperscript{2,3} Canine and human MMVD have a similar aetiology and pathophysiology, and the progression of the disease is usually benign in dogs and people.\textsuperscript{3–7} Supraventricular and ventricular arrhythmias have been reported as more common in people with MMVD compared with the general population.\textsuperscript{8,9} It has been speculated that arrhythmias may play a significant role in determining symptoms and may be responsible for the slightly increased risk of sudden death in human patients with MMVD.\textsuperscript{10} The presence of an arrhythmia has been suggested as a potential complication to the condition in the canine population as well,\textsuperscript{2} but to our knowledge there are no studies investigating the presence of arrhythmias in dogs with MMVD with different classes of heart failure (HF). Recently, we described the occurrence of sudden death in dogs with MMVD that had exhibited no clinical signs.\textsuperscript{7}

The aims of this prospective study were to evaluate the presence of ventricular and supraventricular arrhythmias in small-breed dogs with MMVD, with and without clinical signs of HF, to study the association between the presence of arrhythmias and left atrial enlargement.

**Materials and methods**

**Study design**

The study prospectively enrolled 40 privately owned dogs, weighing less than 20 kg, examined at two cardiology reference centres (Dipartimento di Patologia Animale, Facolta’ di Medicina Veterinaria, Universita’ di Torino, n = 23; Clinica Veterinaria Malpensa, Varese, Italy, n = 17). The dogs had been presented for cardiology consultation either because of the presence of a heart murmur or because of clinical signs indicating a cardiovascular disorder (e.g. cough, dyspnoea, exercise intolerance).
Inclusion criteria. To be included in the study, dogs in the MMVD group had to have at least one of the following abnormalities: mitral valve prolapse (MVP), any subjective degree of mitral valve leaflet thickening on 2-D echocardiography and/or any degree of mitral valve regurgitation, with or without mitral valve lesions, on colour Doppler examination.

Exclusion criteria. Dogs were excluded if they had congenital heart diseases or acquired cardiovascular disorders that primarily or secondarily affect the mitral valve (e.g. bacterial endocarditis, dilated cardiomyopathy).

In each dog, the severity of HF was classified according to the International Small Animal Cardiac Health Council (ISACHC) system and the echocardiographic findings. Dogs were grouped as preclinical (MMVD and no clinical signs: ISACHC classes 1a and 1b) or clinical (MMVD and clinical signs: ISACHC classes 2 and 3). The clinical group of dogs comprised those presenting with clinical signs of HF at the time of the Holter and electrocardiographic (ECG) studies and documented pulmonary oedema on thoracic radiographs, or dogs requiring chronic therapy for the management of MMVD and had had previous episodes of pulmonary oedema documented by thoracic radiography.

Echocardiography

All dogs underwent complete echocardiographic examination, which included transthoracic 2-D, M-mode, spectral and colour flow Doppler studies. Examination was performed in conscious, unsedated dogs. Right parasternal M-mode recordings were obtained from short-axis views with the dogs positioned in right lateral recumbency and the 2-D echocardiograms were obtained in accordance with techniques described elsewhere. The presence of MVP and mitral valve thickening was evaluated from the right parasternal long-axis, right parasternal 4-chamber and left apical 4-chamber views. MVP was defined as any systolic displacement of one or both mitral valve leaflets basal to the mitral annulus observed in at least two views. Mitral valve regurgitation was evaluated using colour Doppler from the right parasternal long-axis and left apical views. The left atrial to aortic root ratio (LA/Ao) was calculated using the 2-D short-axis view as described previously.

Electrocardiography

A high-quality 1-min paper ECG recording was obtained in all dogs (ESAOTE Biomedica P80 Power, Easyview ATES Medica Device, Verona, Italy). The examination was performed in conscious, unsedated dogs lying in right lateral recumbency. All dogs were restrained on a comfortable surface in a quiet environment. The electrodes were placed as described elsewhere and a 12-lead ECG was recorded after a few minutes when the dog appeared relaxed. The recording time varied, with a minimal recording time of 3 min. For each ECG recording the mean HR was calculated during a 6-s period and the presence of arrhythmias was recorded.

Holter monitoring

Holter recordings were obtained and analysed at the two centres using different software programs. Two types of digital Holter recorder with real-time analysis were used for 24 h: Delmar Aria® Digital Holter Recorder (Spacelabs Healthcare, Issaquah, WA, USA) or Cardioline CUBE Holter (et Medical Devices, Italy). The number and position of thoracic electrodes differed between the two systems: one system had four electrodes placed at the level of the base and apex in each
hemithorax and the other system had seven electrodes that were placed according to the corrected Frank lead system. The 24-h monitoring was conducted while the dogs were kept at home. The owners were requested to keep a brief diary describing any major events. Holter data were subsequently transferred to a hard drive for automatic analysis. Two experienced operators (S.C. and R.A.S.) manually edited all the data analyses and corrected the QRS template, including possible misinterpretation for horizontal and vertical resolution, checking the digital 24-h editing program. A crossed analysis of the recordings by the two operators was not performed.

Data obtained from the Holter report included minimum, medium and maximum HR (HRmin, HRmean, HRmax), the number of ventricular premature complexes (VPC), couplets and triplets, ventricular bigeminy or trigeminy, ventricular tachycardia (VT), supraventricular tachycardia (SVT) and atrial fibrillation (AF). The presence of single atrial premature complexes (APC) recorded with Holter monitoring was not analysed because the pronounced sinus arrhythmia and the presence of artefacts made evaluation of the number of APC in the 24 h unreliable. Arrhythmias found during Holter analysis were divided into two main groups: ventricular arrhythmias (VPC, couplets, triplets, ventricular bigeminy or trigeminy and sustained or non-sustained VT) or supraventricular arrhythmias (sustained and non-sustained SVT, AF). VT was defined as a sequence of more than three consecutive large QRS complexes, with HR >180 beats/min and atrioventricular dissociation. SVT was defined as a sequence of more than three consecutive narrow QRS complexes with regular RR intervals, HR >200 beats/min and no evidence of P wave. Any arrhythmia longer than 30 s was defined as sustained. Sinus arrhythmia and sinus tachycardia were not included in the statistical analysis because they were not considered pathological rhythms.

Statistical analysis

The statistical evaluation was done using a computerised statistics program (R 2.3.0; The R Development Core Team: http://www.r-project.org). The normality was tested with the Shapiro-Wilk test. The data are reported as the median and interquartile range.

Differences between group median values were tested with the Wilcoxon rank sum test. Differences between median values of Holter HRmin, HRmean and HRmax were compared between different groups with the pairwise Wilcoxon rank sum test using the Bonferroni P correction (α= 0.05). The presence of arrhythmias in the different groups of HF and in patients with different LA/Ao values was evaluated with Fisher's exact test. The level of significance for all tests was set at P < 0.05.

Results

Study population

Of the 40 dogs with CMVD included in the study, 4 were excluded because a full 24-h recording was not obtained. The final study population comprised 36 dogs of different breeds: 23 mixed breeds, 3 Cocker Spaniels, 2 Pomeranians and 1 each of English Setter, Yorkshire Terrier, Collie, Welsh Terrier, Poodle, Cavalier King Charles Spaniel, Bloodhound and Shih-tzu (27 males, 9 females). The preclinical group included 8 (57.1%) males and 6 (42.9%) females (median age
11.5 ± 3.75 years, mean weight 13.33 ± 5.01 kg; Table 1) and the clinical group included 19 (86.4%) males and 3 (13.6%) females (median age 12 ± 3 years, mean weight 11.06 ± 5.06 kg; Table 2). There were no differences between the two groups for body weight or age.

Table 1. Preclinical group: signalment, ECG, Holter and left atrial dimensions expressed as left atrial/aortic root (LA/Ao) ratio measured on B-mode echocardiography

<table>
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<th>Breed</th>
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<th>Sex</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>ECG diagnosis</th>
<th>ECG HR (beats/min)</th>
<th>Holter diagnosis</th>
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- HRmin, Holter minimum heart rate; HRmean, Holter mean heart rate; HRmax, Holter maximum heart rate; AVB, atrioventricular block;
- ISACHC, International Small Animal Cardiac Health Council severity; SVT, supraventricular tachycardia;
- SVT-s, sustained supraventricular tachycardia; APC, atrial premature complex; VPC, ventricular premature complex;
- BIG, ventricular bigeminy; TRIG, ventricular trigeminy; N, data not available.

Table 2. Clinical group: signalment, ECG, Holter and left atrial dimensions expressed as left atrial/aortic root (LA/Ao) ratio measured on B-mode echocardiography

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<th>ID</th>
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<th>Body weight (kg)</th>
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- HRmin, Holter minimum heart rate; HRmean, Holter mean heart rate; HRmax, Holter maximum heart rate; AVB, atrioventricular block;
- CKCS, Cavalier King Charles Spaniel; ISACHC, International Small Animal Cardiac Health Council severity;
- SVT, supraventricular tachycardia; SVT-s, sustained supraventricular tachycardia; APC, atrial premature complex;
- VPC, ventricular premature complex; BIG, ventricular bigeminy; TRIG, ventricular trigeminy; pAF, paroxysmal atrial fibrillation.

### Echocardiography

The LA/Ao ratio was not available for five dogs in class ISACHC 1 because of corruption of the recorded digitalised cine loops. LA/Ao was significantly higher in the clinical group (2.34 ± 0.37 vs 1.40 ± 0.22, P = 0.0002).

### Standard ECG recording

The median HR was 155 ± 38.75 beats/min and 147.5 ± 50 beats/min in the preclinical and clinical groups, respectively. In the preclinical group 5 dogs (33%) presented with non-sustained SVT, 2 dogs (14%) had VPCs, 1 dog (7%) had APCs and 1 dog (7%) had first- and second-degree AV block (Table 1). In the clinical group 6 dogs (27%) presented with APCs, 5 (23%) had VPCs, 3 (14%) had SVT, 4 (18%) had AF and 1 dog (4%) had non-sustained VT (Table 2).

### Holter monitoring

The preclinical group of dogs had a median HRmin 55 ± 19.5 beats/min, HRmean 88.5 ± 17.5
beats/min and HRmax 189 ± 51 beats/min, compared with 70 ± 21.5, 122 ± 24.5 and 191 ± 19.25 beats/min, respectively, in the clinical group of dogs.

In the preclinical group, 7 dogs (50%) had supraventricular arrhythmias (6 had non-sustained SVT, 1 had sustained SVT) and 8 (57%) had ventricular arrhythmias (8 VPC, 2 ventricular bigeminy and 1 ventricular trigeminy) (Table 1). Of these dogs, 3 (21%) presented with both supraventricular and ventricular arrhythmias. One dog presented with an episode of ventricular bigeminy, 4 beats long, with HR 132 beats/min and an episode of ventricular trigeminy, 8 beats long, with HR 152 beats/min; another dog presented with 136 episodes of ventricular bigeminy, the longest of which was 26 beats with a maximum HR of 201 beats/min. In the clinical group 16 dogs (72%) had supraventricular arrhythmias (13 non-sustained SVT, 3 AF, 1 paroxysmal AF) and 19 dogs (86%) with ventricular arrhythmias (19 VPC, 1 non-sustained VT) (Table 2). Among this group, 15 (68%) had both supraventricular and ventricular arrhythmias (Figure 1). In the dog with paroxysmal AF, the arrhythmia lasted 36 min, with a mean HR of 195 beats/min. The number of VPCs varied between groups; in the preclinical dogs it ranged between 1 and 347, whereas in the clinical group the range was 1–11,862. The numbers of ectopic and normal beats over the 24-h period are summarised in Table 3.

Table 3. Holter data

<table>
<thead>
<tr>
<th>ID</th>
<th>Hours</th>
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<th>SVC</th>
<th>VC</th>
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</table>

Figure 1.

Supraventricular tachycardia (S) and ventricular ectopic beats (V) on a recording from the same dog.
Arrhythmias detected with ECG versus Holter monitoring

In the preclinical group, 1 dog had no arrhythmias on ECG but had SVT on the Holter, 1 dog had APCs on the ECG and SVT on the Holter, 5 dogs showed SVT on the ECG and the Holter confirmed the presence of SVT. In the group of dogs with clinical signs, 6 dogs had no supraventricular arrhythmias on ECG but had SVT during the 24-h monitoring, 4 dogs had APCs on ECG and SVT on the Holter, 3 dogs had SVT on both the ECG and Holter, and 2 dogs had APCs on the ECG but did not have any SVT during Holter monitoring.

Comparison between groups of HF and ECG, Holter and echocardiography values

The HR recorded with standard ECG did not significantly differ between the two groups of dogs. The average HR recorded with the ECG was significantly higher in the preclinical group of dogs (P < 0.001) than in the clinical group (P < 0.005) compared with the mean HR recorded during the 24-h period of monitoring with the Holter.

The HRmin and HRmean were lower in the preclinical group of dogs compared with the clinical group (P = 0.04). No difference was seen between the two groups for the values of HRmax.

There were no differences between the two groups for the overall presence of arrhythmias (supraventricular and ventricular) on both standard ECG and Holter monitor.

Supraventricular and ventricular arrhythmias in the two groups were evaluated separately. No difference was detected for the presence of supraventricular ectopic events. Ventricular arrhythmias...
were more common in the clinical group of dogs than in the preclinical group (P = 0.01; odds ratio = 6.62). There were 3 supraventricular arrhythmias and 8 ventricular arrhythmias in those with LA/Ao <1.7, and 16 and 17, respectively, in the LA/Ao >1.7 group. This was significantly higher for the supraventricular events (P < 0.05, odds ratio 6.9) but not ventricular events.

Discussion

The results of this study show that arrhythmias are a common finding in dogs affected by MMVD with differing severity of HF, and that an enlarged left atrium is associated with an increased risk of supraventricular arrhythmias. The study also shows that the presence of arrhythmias in patients with MMVD is rarely associated with clinical signs, as judged by the owners, including weakness, lypotimia (defined as a transient and sudden onset of weakness, without loss of consciousness)17,18 or syncope.

Frequent arrhythmias were detected in these dogs with MMVD, regardless of the class of HF, a result that is comparable with what has been described in human patients. De Maria et al. found that fewer patients with MMVD were free of arrhythmias compared with the normal population.8 A higher number of supraventricular and ventricular ectopic beats in people with MMVD were also detected in the Framingham study, although the difference compared with the general population was not significant.9,19 A previous study found that the presence of arrhythmias in Dachshunds with preclinical MMVD was more common, compared with dogs without MMVD, but the correlation between arrhythmias and class of HF was not investigated.20

We evaluated the presence of ventricular and supraventricular events separately. The proportion of dogs with ventricular arrhythmias was higher in the clinical group, even if many preclinical patients showed ventricular events during the Holter monitoring. In human medicine, several hypotheses have been proposed to explain ventricular rhythm disturbances in patients with MVP. Ventricular endocardial fibrosis is a common finding in both symptomatic patients and those who die suddenly.21,22 Other proposed mechanisms causing ventricular ectopy include chordal traction by redundant leaflets,23 mechanical stimulation of the endocardium by prolapsing leaflets,24 ventricular dilation and stretch with increased myocardial wall strain.25 It is thought that the cause of arrhythmias in patients with mitral valve disease is probably multifactorial. In the advanced stage of the disease, because of progression of the volume overload, ventricular events become more pronounced. However, in our study an increase in left atrial dimensions was not associated with an increased risk of ventricular arrhythmias.

We hypothesised that a higher number of supraventricular arrhythmias in dogs with left atrial enlargement would correlate with stretching of the left atrium. The LA/Ao ratio was higher in the clinical group of dogs, although there was no difference between the two groups of dogs for supraventricular events. We have previously reported that left atrial enlargement is an independent predictor of the severity of MMVD7 and our present study showed that dogs with LA/Ao >1.7 had more supraventricular rhythm disturbances, suggesting that increased severity of the disease is associated with an increased risk of developing arrhythmias.
Four dogs, all in the clinical group, presented with sustained or paroxysmal AF and all of them had LA/Ao >2. Several studies using experimental canine models of mitral regurgitation have found that chronic volume overload causes the atrial remodelling that leads to a substrate in which AF can be easily induced. Moreover, the most recent study found that the left atrial posterior wall showed the most extensive interstitial fibrosis and the earliest disorganised activity, which plays a role in the induction of AF. This could be related to the fact that, in dogs, prolapse of the anterior mitral valve leaflet is more common than prolapse of the posterior one, which creates a jet directed towards the posterior left atrial wall, thus causing the myocardial instability. Many of the dogs in the present preclinical and clinical groups showed no supraventricular arrhythmias or few APCs during ambulatory ECG, but in the same patients the Holter recording showed runs of SVT, which confirms the higher sensitivity of Holter monitoring in detecting arrhythmias in dogs.

The HR recorded with the standard ECG showed no differences between the two groups of dogs. The ECG HR was significantly higher than the HRmean recorded by the Holter in all dogs, which is not a surprising result, because during the clinical examination the animals were more stressed by the unfamiliar environment, even if the ECG was recorded in a quiet room and measures were taken to reduce stress. This result is similar to a report by Miller et al. in a retrospective study of 44 cases of syncope in dogs. Nevertheless, our 24-h analysis showed no difference between the groups for HRmax, but the HRmin and the HRmean were significantly higher in the clinical group. This result suggests that there was sympathetic activation in the more severe cases of MMVD whereas the preclinical group of dogs had a normal balance between sympathetic and parasympathetic activities. However, this hypothesis should be confirmed by analysis of HR variability, which we did not perform in this study. Nevertheless, our result shows that evaluation of HR by standard ECG should be interpreted with caution when making therapeutic decisions, especially when evaluating dogs treated with an antiarrhythmic drug (such as digoxin) for HR control.

Study limitations

The major limitation is the lack of an age-matched control group. It is unknown if the same number of arrhythmias would occur in an age-matched control group without MMVD. However, considering the high prevalence of MMVD in small-breed dogs over 8 years of age, it is difficult to create a group of dogs, matched for age and weight, without mitral valve lesions. Another limitation is the lack of uniformity in the time period of inclusion. All dogs were included over a period of 2 years, regardless of the season. It is possible that ambient conditions and temperature could influence HR in dogs. However, to the best of our knowledge, it is unknown if weather conditions have any influence on Holter recording or ECG abnormalities in dogs. Finally, the study was conducted at two clinics with two different Holter systems and the data were analysed by two different operators. However, the analysis was manually edited by two skilled operators, which should compensate for the variability related to the use of different software.

Conclusions

Our study results show that Holter monitoring is superior to standard ECG in detecting arrhythmias and evaluating HR in dogs with preclinical or clinical MMVD. We found a large percentage of dogs
with MMVD presented with several supraventricular and ventricular rhythm disturbances. An enlarged left atrium is associated with a higher risk of supraventricular events and the clinical group of dogs appeared to present more commonly with more ventricular arrhythmias than dogs without clinical signs. To the best of our knowledge, this is the first study to evaluate the presence of arrhythmias in dogs affected by MMVD by using Holter monitoring. Further studies are required to evaluate if the presence of arrhythmias in dogs with MMVD has any effect on progression of the disease and survival.

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**References**


