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*Original Article*

# Electrocardiographic Changes in Dogs with Degenerative Mitral Valve Disease Treated with Pimobendan: a Retrospective Study of 29 Cases

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***Abstract***

The aim of this retrospective study was to evaluate changes in electrocardiograms (ECG) and cardiac arrhythmias in 29 dogs with degenerative mitral valve disease (DMVD) treated with pimobendan chronically. All dogs had normal ECG before pimobendan administration. The dogs were classified according to ECG after pimobendan administration into 2 groups: normal ECG (n=19) and abnormal ECG (n=10). Age, sex, breed, serum alkaline phosphatase, concurrent digoxin administration, total daily dosage of pimobendan and digoxin, duration of pimobendan administration, and ECG parameters including heart rate, P wave, PR interval, QRS complex, and QT interval were analyzed. Cardiac arrhythmias were increasingly found in the dogs treated with pimobendan in combination with digoxin. The total daily dosage of pimobendan and digoxin in the dogs with abnormal ECG was higher than in those with normal ECG ($p$=0.022, 0.038, respectively). In conclusion, cardiac arrhythmias can be found in dogs chronically treated with pimobendan. Therefore, caution should be taken when using pimobendan at a high dosage or in combination with digoxin.

**Keywords:** arrhythmia, canine, digoxin, pimobendan

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## Introduction

Several studies in human patients reported that some of the positive inotropic agents might have pro-arrhythmic effects (Felker and O'Connor, 2001; Packer et al., 1991). In veterinary medicine, studies evaluating pro-arrhythmic effects of positive inotropic drugs are scarce. Presently, positive inotropes such as pimobendan and digoxin have been widely prescribed in dogs with congestive heart failure, including the most common disease, degenerative mitral valve disease (DMVD) (Summerfield et al., 2012; Haggstrom et al., 2013[a]; Kanno et al., 2007).

Pimobendan (4,5 –dihydro-6-[2- (4-mrthoxyphenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone), a benzimidazole-pyridazinone derivative, increases the myocardium contractility by inhibiting phosphodiesterase 3 and 4 enzymes, decreasing an elimination of cyclic adenosine 3',5'-monophosphate (cyclic AMP), and ultimately increasing calcium within the cytosol of the myocardium. Pimobendan also enhances the myocardial contractility without an increase in myocardial oxygen demand by augmenting the sensitivity of troponin C to calcium, which is called the calcium sensitizing property (Fitton and Brogden, 1994). This property of pimobendan is different from cardiac glycosides such as digoxin and catecholamines (Matos and Glaus, 2010). Moreover, pimobendan acts as a vasodilator by increasing the cyclic AMP within the endothelial cells, facilitating calcium uptake through intracellular storage sites, thereby decreasing the amount of calcium available for contraction, resulting in vasodilation (McDaniel et al., 1994). It has been believed that pimobendan has a low calcium-mediated pro-arrhythmic effect because pimobendan acts as a calcium sensitizer with a minimal effect on an increase in calcium concentration in the myocardium (Ruegg, 1986). Nowadays studies evaluating pro-arrhythmic effects of pimobendan are sparse and conflicting. A previous study reported that pimobendan had an acute effect on electrophysiological properties of the myocardium and atrioventricular (AV) node (Kitzen et al., 1988). Human patients treated by pimobendan had a trend toward higher risk of sudden death, presumably secondary to cardiac arrhythmias (Felker and O'Connor, 2001; Lubsen et al., 1996). An adverse effect of pimobendan inducing cardiac arrhythmias in giant dog breeds has been suggested (Rosenthal et al., 2006). Several studies reported evidence of cardiac arrhythmias in dogs treated with pimobendan; however, the frequency and incidence of arrhythmias were not different when compared with dogs treated with the other drug, benazepril (Haggstrom et al., 2008; Haggstrom et al., 2013[a]). A short-term pilot study did not find any significant difference in the incidence or types of arrhythmia between degenerative mitral valve disease (DMVD) dogs treated with pimobendan and a placebo (Lake-Bakaar et al., 2015). However, most of these studies were performed over limited time periods, i.e. not more than 2 months, and were not designed for evaluating a pro-arrhythmic effect of pimobendan. To the authors' knowledge, a long-term effect of pimobendan on cardiac arrhythmias in dogs with heart diseases has not been studied yet. Therefore, the aim of this study was to evaluate long-term effects of pimobendan on electrocardiographic changes and cardiac arrhythmias in dogs affected by DMVD.

## Materials and Methods

From February 2010-November 2014, clinical data on dogs diagnosed with DMVD stage C at the Cardiology Clinic, Small Animal Veterinary Teaching Hospital, Chulalongkorn University, Thailand were studied. The dogs had been diagnosed with DMVD by an echocardiographer (SS) and staged using the American College of Veterinary Internal Medicine (ACVIM) classification (Atkins et al., 2009). Echocardiography, radiography, and electrocardiography (ECG) were performed on the day of the DMVD diagnosis before the administration of pimobendan. All the dogs were treated with pimobendan at an average dosage of 0.39±0.15 mg/kg per day. Data on the patients including age, sex, weight, breed, alkaline phosphatase levels, concurrent use of digoxin, total daily dosage of pimobendan and digoxin, duration of pimobendan administration, ECG before and after treatment with pimobendan, and time of pimobendan treatment before the occurrence of arrhythmias were collected. Electrocardiographic records obtained from a three-minute Lead II tracing were evaluated. Duration and amplitude of P wave, QRS complex, and T wave as well as PR and QT intervals were measured randomly and averaged from 10 consecutive waves. QT and corrected QT (QTc) intervals were measured and calculated, using Van de Water's equation QTc = (QT - 0.087 * [(60 / HR) - 1] (Van de Water et al., 1989). Dogs with abnormal ECG prior to pimobendan treatment were excluded from the study. Newly diagnosed cardiac arrhythmias after treatment with pimobendan were recorded.

*Statistical analysis*

Statistical analyses were performed using a commercial statistical software (Minitab®17, State College, PA, USA). The patient data including age, sex, weight, breed, and alkaline phosphatase levels were reported descriptively. Normality of the data was tested by the Shapiro-Wilk. Normally distributed data were presented as mean±standard deviation (SD). In dogs with normal ECG after pimobendan administration, ECG parameters including P wave, QRS complex, T wave durations and amplitudes, and duration of PR and QTc intervals were compared before and after pimobendan treatment by a paired *t* test. Effects of the treatment duration, breeds of dogs, and concurrent use of digoxin on an evidence of ECG abnormalities were evaluated by Fisher's exact test. The dosage per day of pimobendan and digoxin and the treatment duration of dogs with normal and abnormal ECG after pimobendan treatment were compared by an unpaired *t*-test. Differences at *p*-value $<0.05$ were considered significant.

## Results

The data of twenty-nine dogs met the inclusion criteria. Nineteen dogs had normal ECG and ten dogs had abnormal ECG after treated with

pimobendan. The information on the dogs is summarized in Table 1.

In the dogs with normal ECG after treated with pimobendan, there was no difference in the P wave, QRS complex, T wave durations and amplitudes, and duration of PR and QTc intervals before and after being treated with pimobendan alone (Table 2) and pimobendan in combination with digoxin (Table 3).

The data of dogs with abnormal ECG after being treated with pimobendan are summarized in Table 4. Eight of the ten dogs had increased alkaline phosphatase after being treated with pimobendan. Only three dogs had higher levels more than five times of normal limits.

**Table 1** Information on 29 dogs included in the study

| | **Total dogs (n=29)** | **Dogs with normal ECG after treated with pimobendan (n=19)** | **Dogs with abnormal ECG after treated with pimobendan (n=10)** |
|---|---|---|---|
| Age (year)* | 12.9±2.5 | 13.3±2.7 | 12.3±2.2 |
| Weight (Kg)* | 7.4±5.6 | 6.2±4.6 | 9.6±6.7 |
| Sex | Male=18 (62.1%)<br>Female=11 (37.9%) | Male=11 (57.9%)<br>Female=8 (42.1%) | Male=7 (70.0%)<br>Female=3 (30.0%) |
| Small breeds | 21 (72.4%)<br>Shih Tzu (8), Poodle (7), Miniature pinscher (2), Splitz (1), Pekingese (1), Pomeranian (1), Chihuahua (1) | 15 (78.9%)<br>Shih Tzu (6), Poodle (4), Miniature Pinscher (2), Splitz (1), Pekingese (1), Chihuahua (1) | 6 (60.0 %)<br>Poodle (3), Shih Tzu (2), Pomeranian (1) |
| Middle breeds | 8 (27.6%)<br>Mixed (6), Bangkeaw (1), Basset hound (1) | 4 (21.1%)<br>Mixed (3), Basset hound (1) | 4 (4.0%)<br>Mixed (3), Bangkeaw (1) |
| Digoxin | | | |
| Treated | 14 (48.3%) | 6 (31.6%) | 8 (80.0%) |
| Not treated | 15 (51.7%) | 13 (68.4%) | 2 (20.0%) |
| Dosage (mg/kg/d) | | | |
| Pimobendan | 0.39±0.15 | 0.35±0.15 | 0.47±0.12 |
| Digoxin | 0.007±0.002 (n=14) | 0.005±0.001 (n=6) | 0.008±0.003 (n=8) |

*Data presented as mean±standard deviation (SD)

**Table** 2 Comparison of electrocardiography before and after treated with pimobendan alone in DMVD dogs with normal ECG (n=13)

| | **Before** | **After** | ***p*-value** |
|---|---|---|---|
| Heart rate (b/m) | 116±23 | 126±23 | 0.12 |
| P wave | | | |
| Amplitude (mV) | 0.29±0.11 | 0.26±0.12 | 0.49 |
| Duration (sec) | 0.05±0.01 | 0.04±0.01 | 0.16 |
| PR interval (sec) | 0.09±0.03 | 0.10±0.04 | 0.51 |
| QRS complex | | | |
| Amplitude (mV) | 1.99±0.95 | 1.71±0.62 | 0.30 |
| Duration (sec) | 0.04±0.03 | 0.04±0.06 | 0.34 |
| QTc interval (sec) | 0.16±0.06 | 0.16±0.08 | 0.56 |

Data presented as mean±standard deviation (SD)

**Table** 3 Comparison of electrocardiography before and after treated with pimobendan in combination with digoxin in dogs with normal ECG (n=6)

| | **Before** | **After** | ***p*-value** |
|---|---|---|---|
| Heart rate (b/m) | 134±26 | 131±21 | 0.81 |
| P wave | | | |
| Amplitude (mV) | 0.32±0.09 | 0.25±0.13 | 0.39 |
| Duration (sec) | 0.04±0.01 | 0.04±0.01 | 0.36 |
| PR interval (sec) | 0.10±0.03 | 0.12±0.01 | 0.61 |
| QRS complex | | | |
| Amplitude (mV) | 2.08±0.46 | 1.84±0.58 | 0.29 |
| Duration (sec) | 0.05±0.02 | 0.04±0.01 | 0.26 |
| QTc interval (sec) | 0.19±0.11 | 0.18±0.02 | 0.78 |

Data presented as mean±standard deviation (SD)

Five dogs were treated with pimobendan for a month. Two out of these dogs had abnormal ECG. Eight of fourteen dogs treated with pimobendan for more than a month had abnormal ECG. Six of the twenty-one small breeds and four of the eight middle breeds had abnormal ECG. There was no effect of the

treatment duration (30 days versus >30 days) (p=0.211) and breed (small versus middle breeds) (p=0.348) on the development of abnormal ECG. The duration of pimobendan administration was not different between the dogs with normal ECG (202±47 days) and abnormal ECG (333±74 days) (p=0.155). The dogs treated with pimobendan in combination with digoxin had a higher risk of developing abnormal ECG than the dogs treated with pimobendan alone (p=0.013) (Table 1). The dogs with abnormal ECG were treated with a higher dosage per day of digoxin and pimobendan than the dogs with normal ECG (p=0.038, p=0.022, respectively) (Table 1).

**Table** 4 Information on dogs with abnormal electrocardiography after treated with pimobendan

| Age (year) | Breed | Digoxin | Duration of pimobendan supplementation (month) | Alkaline phosphatase | | Electrocardiography | | Severe LA enlargement (LA:Ao ratio>2) |
|---|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before receiving pimobendan | After receiving pimobendan | |
| 16 | Shih Tzu | N | 1 | 254 | 65 | Respiratory arrhythmia | 2nd degree AV block | Y |
| 11 | Poodle | N | 1 | 63 | 104 | Sinus rhythm | Atrial fibrillation | Y |
| 11 | Bangkeaw | Y | 2 | 102 | 65 | Respiratory arrhythmia | Junctional premature beat | N |
| 13 | Mixed | Y | 5 | 19 | 36 | Sinus rhythm | Atrial fibrillation with VPCs | Y |
| 13 | Poodle | Y | 8 | 184 | 353 | Sinus rhythm | 2nd degree AV block | N |
| 14 | Mixed | Y | 10 | 148 | 735 | Sinus rhythm | Sinus tachycardia* | N |
| 14 | Poodle | Y | 14 | 107 | 223 | Sinus rhythm | Sinus tachycardia* | N |
| 11 | Mixed | Y | 14 | 86 | 159 | Respiratory arrhythmia | Sinus tachycardia* | N |
| 12 | Pomeranian | Y | 15 | 78 | 190 | Sinus rhythm | Atrial fibrillation | N |
| 8 | Shih Tzu | Y | 16 | 264 | 319 | Respiratory arrhythmia | Atrial fibrillation | Y |

LA=Left atrium; Ao=aorta; Y=yes; N=no

*Sinus tachycardia was defined as heart rate more than 200 beat/min.

## *Discussion*

The major finding of this study is that cardiac arrhythmias can be found in dogs chronically treated with pimobendan, especially in dogs treated with a higher dosage of pimobendan and/or in combination with digoxin.

The earliest time to detect cardiac arrhythmias in the population of dogs in this study was a month after the pimobendan treatment. Types of cardiac arrhythmias included atrial fibrillation, sinus tachycardia, second degree AV block, ventricular premature beat, and junctional premature beat. These arrhythmias were similar to the evaluation study of safety and effectiveness of pimobendan (Vetmedin, 2007). The majority of dogs with cardiac arrhythmias in the present study had atrial fibrillation. The mechanism of pimobendan-induced atrial fibrillation has not been reported. Severe left atrial enlargement may be a potential cause of atrial fibrillation in 3 of 4 dogs in the present study. It is possible that atrial fibrillation may occur secondarily to the disease progression rather than being a direct effect of pimobendan itself. Pimobendan has a dose-dependent increase in heart rate secondary to an increase in intracellular cAMP in cardiac tissues (Hagemeijer, 1993; Chu et al., 1995). One study reported severe sinus tachycardia in dogs administered with a high dose of pimobendan (Reinker et al., 2012). Three dogs in the present study had sinus tachycardia (heart rate >200 beats/min) after approximately a year of treatment with pimobendan. In contrast, several studies failed to report the evidence of pimobendan-induced sinus tachycardia (Smith et al., 2006; Haggstrom et al., 2013b). Second degree AV block and junctional premature beat in three dogs in the present study may occur secondarily to the effect of pimobendan on function of the AV node (Kitzen et al., 1988). One dog in the present study had ventricular premature complex (VPC). It has been concerned that phosphodiestase III inhibitors like pimobendan may exacerbate the development of ventricular arrhythmias (Lynch et al., 1988; Rosenthal et al., 2006). However, a recent study could not find difference in VPCs number/24 h between dogs treated with pimobendan and a placebo (Lake-Bakaar et al., 2015). Several studies demonstrated that there was no difference in VPC numbers and incidence of ventricular arrhythmias when compared between dogs treated with pimobendan and angiotensin converting enzyme (ACE) inhibitors (Smith et al., 2006; O'Grady et al., 2004). Based on the results of those previous studies, the effect of pimobendan-induced VPCs is still controversial. In the present study, some dogs with abnormal ECG had high levels of alkaline phosphatase after being treated with pimobendan. According to the safety study, pimobendan can cause a mild elevation of alkaline phosphatase levels (Vetmedin, 2007). It has

been suggested that alkaline phosphatase may increase due to a major elimination pathway of pimobendan through bile excretion (Plumb, 2008).

Presently, there are few studies determining the pro-arrhythmic effects of pimobendan in veterinary medicine. A previous study showed that dogs treated with higher doses of pimobendan had a higher risk of developing cardiac arrhythmias (Summerfield et al., 2012). Similarly, the present study showed that the dogs with abnormal ECG were treated with a higher dosage of pimobendan than those with normal ECG. However, the present study failed to show the effect of breed (small versus medium breeds) on pimobendan-induced cardiac arrhythmias. A previous study showed that giant dog breeds had a higher risk of developing cardiac arrhythmias after treatment with pimobendan (Rosenthal et al., 2006). Unfortunately, none of the giant breeds was included in the present study.

The dogs treated with pimobendan in combination with digoxin had a higher risk of developing cardiac arrhythmias than those treated with pimobendan alone. The dogs with cardiac arrhythmias were also treated with a higher dosage of digoxin. Digoxin itself can cause cardiac arrhythmias secondary to its toxicity (Steiness and Olesen, 1976). However, all dogs developing cardiac arrhythmias in this study had digoxin levels (1.5±0.5 ng/ml) within the normal limit (0.5- 2 ng/ml) and presented no sign of digoxin toxicity, e.g. diarrhea, anorexia, and vomiting. Presently, there was no report studying the synergist effect of pimobendan and digoxin on induced cardiac arrhythmias. In theory, pimobendan may increase the rate of intestinal digoxin absorption (Aiba et al., 2005). However, clinically, there is no report evaluating the effects of pimobendan on digoxin absorption or serum digoxin concentration.

Because the study was retrospective, there were several limitations that could not be controlled. Firstly, the present study was performed without a control group; thus, the effect of worsening disease severity was not accounted for. Arrhythmias might develop without the effects of pimobendan. Secondly, the monthly follow-up might delay or miss the detection of cardiac arrhythmias in some dogs before the appointment. Thirdly, the data were collected from a small number of dogs, not enough to extrapolate the whole population of dogs. Thus, a prospective study evaluating the long-term effect of pimobendan on ECG changes and electrophysiology with a larger number of dogs should be performed. Lastly, Holter monitoring was not done in the present study. With 3-minute ECG tracings, cardiac paroxysmal arrhythmias might not be detected in some dogs.

In conclusion, cardiac arrhythmias may develop in some dogs treated chronically with pimobendan, especially in dogs treated with a higher dosage of pimobendan and/or in combination with digoxin. ECG monitoring should be performed in dogs chronically administered with pimobendan.

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# บทคัดย่อ

## การเปลี่ยนแปลงของคลื่นไฟฟ้าหัวใจในสุนัขที่เป็นโรคลิ้นหัวใจไมทรัลเสื่อม ที่รักษาด้วยยาพิโมเบนแดน การศึกษาย้อนหลังในสัตว์ป่วย 29 ตัว

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วัตถุประสงค์ของการศึกษาย้อนหลังนี้เพื่อประเมินการเปลี่ยนแปลงของคลื่นไฟฟ้าหัวใจ และการเกิดภาวะหัวใจเต้นผิดจังหวะในสุนัข 29 ตัวที่เป็นโรคลิ้นหัวใจไมทรัลเสื่อมที่รักษาด้วยยาพิโมเบนแดนแบบเรื้อรัง สุนัขทุกตัวมีคลื่นไฟฟ้าหัวใจปกติก่อนได้รับยา แบ่งสุนัขเป็น 2 กลุ่มตามลักษณะของคลื่นไฟฟ้าหัวใจหลังได้รับยาพิโมเบนแดน ได้แก่ กลุ่มที่มีคลื่นไฟฟ้าหัวใจปกติ (n=19) และกลุ่มที่มีคลื่นไฟฟ้าหัวใจผิดปกติ (n=10) ทำการวิเคราะห์ข้อมูล ได้แก่ อายุ เพศ พันธุ์ ค่าเอนไซม์อัลคาไลน์ ฟอสฟาเตส การได้รับยาดิจอกซิน ขนาดของยาพิโมเบนแดนและดิจอกซินที่ได้รับต่อวัน และพารามิเตอร์ต่างๆของคลื่นไฟฟ้าหัวใจ ได้แก่ อัตราการเต้นของหัวใจ คลื่นพี ระยะพีอาร์ คลื่นคิวอาร์เอส และระยะคิวที การศึกษาพบภาวะหัวใจเต้นผิดจังหวะเพิ่มขึ้นในสุนัขที่ได้รับยาพิโมเบนแดนร่วมกับดิจอกซิน ขนาดของยาพิโมเบนแดนและดิจอกซินที่ได้รับต่อวันในสุนัขที่มีคลื่นไฟฟ้าหัวใจผิดปกติสูงกว่าสุนัขที่มีคลื่นไฟฟ้าหัวใจปกติ ($p$=0.022, 0.038 ตามลำดับ) โดยสรุปภาวะหัวใจเต้นผิดจังหวะสามารถพบได้ในสุนัขที่รักษาด้วยพิโมเบนแดนแบบเรื้อรัง ดังนั้นควรระวังการให้พิโมเบนแดนในขนาดสูงหรือการให้ร่วมกับยาดิจอกซิน

**คำสำคัญ:** หัวใจเสียจังหวะ สุนัข ดิจอกซิน พิโมเบนแดน

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