Original Article

Long-term effects of repeated oral dose of ivabradine on heart rate variability in dogs with asymptomatic degenerative mitral valve disease

Prapawadee Pirintr[1] Nakkawee Saengklub[2] Vudhiporn Limprasutr[3] Anusak Kijtawornrat[1,4*]

Abstract

Degenerative mitral valve disease (DMVD) is the most common acquired cardiac disease in geriatric dogs leading to impaired cardiac autonomic activity and functions. This study aimed to evaluate the heart rate (HR), blood pressure (BP), myocardial oxygen consumption ($MVO_{2)}$ and heart rate variability (HRV) of dogs with DMVD stage B2 in response to long-term treatment with ivabradine, orally. Four beagles with naturally occurring DMVD stage B2 were instrumented with a 24-h Holter recorder to obtain electrocardiography and HRV, an oscillometric device to acquire blood pressure (BP), HR and myocardial oxygen consumption (MVO_2) as assessed by rate-pressure product (RPP = HR x Systolic BP). Dogs were given ivabradine (1.0 mg/kg, twice daily, orally) for 3 months. Data were obtained at baseline and every 4 weeks for 12 weeks (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks) after oral administration of ivabradine. The results revealed that chronic administration of ivabradine significantly decreased HR, BP, and RPP without adverse effects ($P < 0.05$). All indices of time- and frequency- domain of HRV at M3 were significantly increased when compared with baseline values ($P < 0.05$). The findings of this study imply that long-term treatment with ivabradine at a dose of 1.0 mg/kg twice daily in dogs with asymptomatic DMVD stage B2 decreased the HR, BP, MVO_2 and improves HRV. This makes ivabradine potentially promising for management of elevated HR and impaired HRV in asymptomatic dogs with DMVD stage B2.

Keywords: dog, heart rate variability, ivabradine, mitral valve degeneration

[1]*Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, 39 Henri Dunant Road, Pathumwan, Bangkok 10330, Thailand*

[2]*Department of Physiology, Faculty of Pharmacy, Mahidol University, 447 Sri Ayudhya Road, Rajathevi, Bangkok 10400, Thailand*

[3]*Department of Pharmacology and Physiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, 254 Phayathai Road, Pathumwan, Bangkok 10330, Thailand*

[4]*Research clusters: research study and testing of drug's effect related to cardiovascular system in laboratory animal, Chulalongkorn University, 39 Henri Dunant Road, Pathumwan, Bangkok 10330, Thailand*

***Correspondence**: anusak.k@chula.ac.th*

Introduction

Degenerative mitral valve disease (DMVD) is the most common acquired heart disease in small breed, aging dogs. Several compensatory mechanisms including the sympathetic nervous system and the renin-angiotensin aldosterone system are triggered when the valve is leaking due to backward flow of blood from the left ventricle into the left atrium (Oyama, 2009). The consequence of the compensatory mechanism of low stroke volume is elevated heart rate (HR) leading to increase myocardial oxygen consumption (MVO_2). Although the compensatory mechanism seems to be helpful in improving cardiac function and maintaining perfusion pressure, it injures the heart and other organs. If there is no intervention, cardiac autonomic nervous system (ANS) imbalance and cardiac malfunction will occur.

In both human and veterinary medicines, cardiac ANS activity can be quantitatively assessed by monitoring HR variability (HRV). It has been shown that lowering HRV has prognostic significance for autonomic impairment (stein et al., 1994; Task Force of the European Society of Cardiology, 1996; Calvert, 1998; Sztajzel, 2004) and mortality in patients with congestive heart failure (CHF) (Karcz et al., 2003). The HRV can be expressed as time- and frequency-domain parameters which reflect the changing sympathetic or parasympathetic activity of the heart (Task Force of European Society of Cardiology, 1996; De Jong and Randall, 2005). Recent publications have demonstrated that HRV is a very sensitive tool for detecting mild mitral regurgitation (MR) in dogs and for monitoring pharmacological treatment (Fujii and Wakao, 2003; Rasmussen et al., 2012; Pirintr et al., 2017). Recent clinical trials in DMVD dogs with MR have suggested that several cardiovascular drugs including enalapril and sildenafil could improve HRV and cardiac function in asymptomatic DMVD dogs (Chompoosan et al., 2014; Kijtawornrat et al., 2017; Pirintr et al., 2017). However, data for using ivabradine in asymptomatic DMVD dogs are not available.

Ivabradine is a pure funny channel blocker that has demonstrated a HR reduction and MVO_2 reduction effect in normal, exercising conscious dogs (Colin et al., 2004). Ivabradine has no veterinary-labeled nor currently approved use for dogs and cats (Bucchi et al., 2007; Rosano et al., 2014; FDA, 2015). The benefits of HR reduction by ivabradine have been demonstrated previously in multicenter clinical trials (Swedberg et al., 2010), but its effect on cardiac function is limited, especially in veterinary medicine.

Autonomic imbalance resulting from sympathetic over activity or parasympathetic withdrawal and cardiac malfunction are characteristic features of CHF. Therefore, the present study hypothesized that early treatment with ivabradine may improve HRV in dogs with asymptomatic DMVD. The aim of this study was to assess the HRV of asymptomatic DMVD dogs in response to long-term treatment with ivabradine.

Materials and Methods

Approvals: This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Chulalongkorn University Laboratory Animal Center (CULAC), Bangkok, Thailand (protocol number: 1673003). All experimental animal procedures were performed in compliance with CULAC IACUC regulation, Animals for Scientific Purposes Act (A.D. 2015) and followed the guidelines outlined in the *Guide for the Care and Use of Laboratory Animals* (NRC, 2011).

Animals: Four beagles (*Canis familiaris*) of both genders (two males, two females) were transferred from a breeding colony of the Department of Obstetric Gynecology and Reproduction, Faculty of Veterinary Science, Chulalongkorn University. They were housed in a group from the time of arrival to the end of the study in a dog run maintained at a temperature between 19°C and 23°C, a relative humidity between 30% and 70%, and a 12-h:12-h dark: light cycle. All animals received commercial diet once a day, and water was provided *ad libitum* in stainless steel containers. Physical examination, routine lead II ECG recording, 2D, M-mode and Doppler echocardiography, thoracic radiograph, complete blood cell count, and blood chemistry analyses were performed to evaluate the health status in all dogs, and to confirm that all dogs were in ACVIM stage B2 before beginning the experiment. None of the dogs were on any pharmacological treatment.

Experimental procedures: Blood collection for hematology and biochemistry profile (i.e. blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase), blood pressure (BP) measurement, electrocardiography (ECG), 24-h Holter recording, and transthoracic echocardiography were performed in all dogs at baseline and every 4 weeks for 12 weeks (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks) after oral administration of 1.0 mg/kg ivabradine twice daily until the end of the study period at 3 months (M3). The clinical variables of all dogs such as appetite, behavior, activity, defecation, urination, vomiting, respiration and BP were evaluated before administering ivabradine each day to monitor adverse reactions (e.g. low BP and bradycardia). In addition, dogs were monitored for at least 15 minutes afterwards to ensure proper drug administration. The dose of ivabradine 1 mg/kg BID P.O. was chosen based on our previous experiment in conscious dogs with asymptomatic DMVD (Pirintr et al., 2018).

Arterial BP measurement was performed 1 hour before 24-h Holter recording. The HR, systolic, diastolic and mean arterial BP were obtained using an oscillometric device (petMAP™, CardioCommand, Inc., Florida, USA). Five consecutive measurements of BP were performed and the mean of three consistent BP values was used (Vachon et al., 2014). In addition, MVO_2 was inferred from the rate-pressure product (RPP), which is calculated as systolic BP multiplied by HR (Nordlander et al., 1989; Cober et al., 2011).

The Holter monitor (Fukuda Denshi Co., Ltd., Japan) was attached to the dogs at indicated time points (baseline, M1, M2 and M3) as previously described (Pirintr et al., 2017). The 24-h continuous ECG was recorded and stored on an SD card for further analysis of HR and HRV using SCM-510 Holter software (Fukuda Denshi Co., Ltd., Japan). All QRS

complexes from ECG were automatically analyzed by the software followed by manually inspection of the correct RR intervals by a single experienced operator. The recording was considered acceptable if 85% or more of raw R waves were normal beats. Signals were filtered through a Hamming window and transformed into a spectrum by fast Fourier transformation. HRV parameters were analyzed from 512 samples of consecutive RR intervals. In this study, the power spectrum consists of frequency bands ranging from 0-0.5 (total power, TP), low frequency (LF) band ranging from 0.041 to 0.15 Hz, and high frequency (HF) band ranging from 0.15 to 0.5 Hz (Pirintr et al., 2012). The frequency-domain parameters of HRV in this study including LF, HF, TP and the ratio of low frequency to high frequency (LF/HF). In addition, the time-domain parameters were evaluated for the mean NN intervals (NNA), standard deviation of all normal to normal RR intervals (SDNN), the standard deviation of 5-minute mean RR intervals (SDANN), the mean of the standard deviation of all normal-to-normal RR intervals for all 5-minute segments (SDNN index), the percentage of successive normal RR intervals exceeding 50 ms (pNN50), and the square root of the mean of the squares of the differences between successive normal to normal RR intervals (rMSSD).

Statistical analysis: All numerical data were presented as mean ± standard error of mean (SEM). The Statistical analyses were performed using commercially available software (IBM SPSS Statistics version 22). HR, systemic BP, RPP, ECG intervals, and HRV parameters were compared among time points (baseline, M1, M2 and M3) using one-way ANOVA with repeated measures followed by Dunnett post-hoc analysis. In all cases, a P value < 0.05 was considered statistically significant.

Results

All four dogs used in this study completed the study period of 3 months without progression of the disease to CHF. All dogs, weighing between 9.85-13.35 kg, are older than 6 years (ranging from 6.2 – 8.2 yr) and presented with systolic murmur grade III-VI/VI. All ECG tracings demonstrated no increase of either supraventricular or ventricular arrhythmias nor changes to ECG intervals and amplitudes after receiving ivabradine, except for the RR interval, which was prolonged after receiving ivabradine (479.73 ± 54.64 ms to 689.50 ± 40.02 ms, P < 0.05). Complete blood count and blood chemistry profiles obtained during the 3-month study period did not demonstrate any clinically abnormal changes. The vertebral heart scores (VHS) obtained from thoracic radiograph were 10.5±0.18 at baseline and 10.5± 0.30 at M3.

Effect of ivabradine on BP, HR and MVO_2: The systolic, diastolic and mean arterial BP at baseline were 169 ± 8.9 mmHg, 104 ± 5.9 mmHg and 128 ± 7.0 mmHg, respectively (Fig. 1). In response to repeated oral dose of ivabradine, systolic and mean arterial BP were significantly lower at M2 (P < 0.05; -9.15 % and –8.93 %, respectively) and M3 (P < 0.05; -15.82 % and –15.48 %, respectively) when compared with baseline; diastolic BP was significantly lower only at M3 (P < 0.05; -14.42 %) when compared with baseline. The BP did not change at M1 when compared with baseline. The HR obtained from the oscillometric device at baseline was 152 ± 4.0 bpm and it was significantly lower at M1 (-10.91 %, P < 0.05), M2 (-18.19 %, P < 0.05) and M3 (-23.30 %, P < 0.05) when compared with baseline (Fig. 2a). The MVO_2 as estimated from rate-pressure product at baseline was 25,779 bpm.mmHg and this was significantly lower at M1 (-12.96 %, P < 0.05), M2 (-25.78 %, P < 0.05) and M3 (-35.55 %, P < 0.05) when compared with baseline (Fig. 2b).

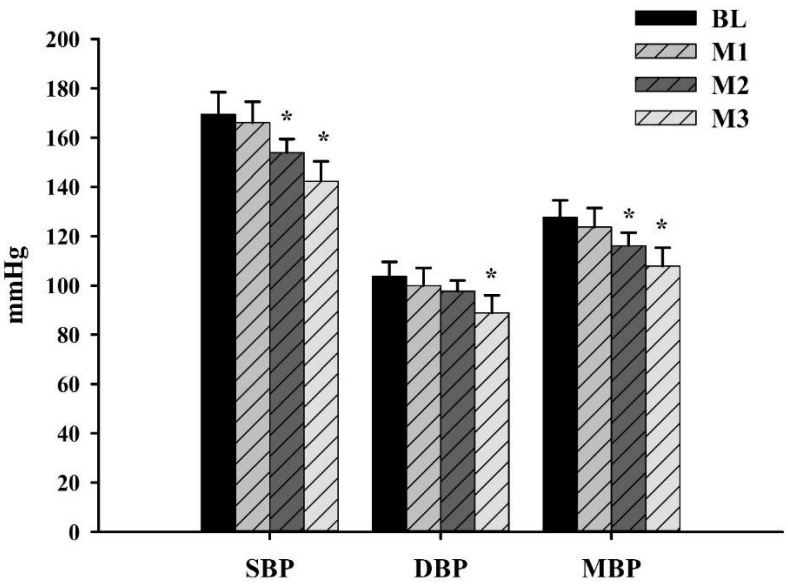

Figure 1 Histogram illustration of an average of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) of dogs with degenerative mitral valve disease obtained at baseline (BL) and after chronic administration of 1 mg/kg ivabradine orally twice a day (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks). *indicates P < 0.05 when compared with baseline, bpm = beat per minute, mmHg = millimeter of mercury.

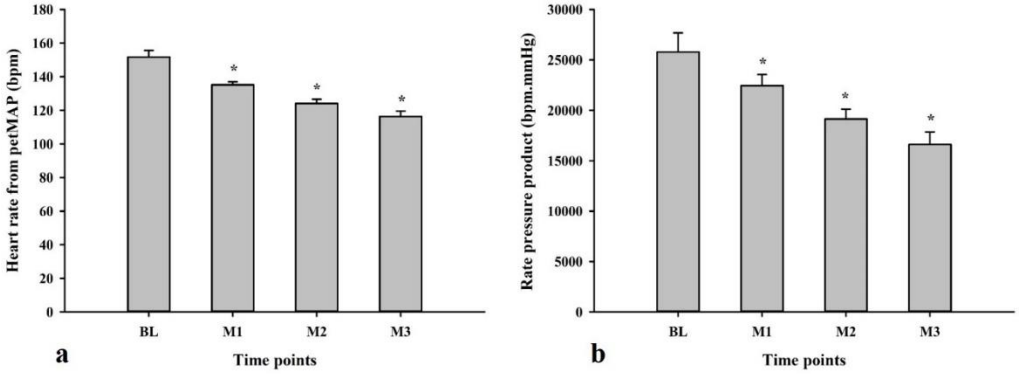

Figure 2 Histogram illustration of an average of heart rate (a) and rate pressure product (b) of dogs with degenerative mitral valve disease obtained at baseline (BL) and after chronic administration of 1 mg/kg ivabradine orally twice a day (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks). *indicates $P < 0.05$ when compared with baseline

Effect of ivabradine on HRV: The mean HR obtained from 24 h continuous ECG recording at baseline was 133 ± 4.0 bpm and it was significantly lower at M1 (-8.3 %, $P < 0.05$), M2 (-12.1 %, $P < 0.05$) and M3 (-17.2 %, $P < 0.05$) when compared with baseline (Fig. 3). The maximum instantaneous HR was unaltered when compared among time points. The minimum instantaneous HR at baseline was 80 ± 4.0 bpm and it was lower at M1 (-8.1 %) and significantly lower at M2 (-11.8 %, $P < 0.05$) and M3 (-15.6 %, $P < 0.05$) when compared with baseline. No dog in any groups had a minimal instantaneous HR below 60 bpm.

The incidence of cardiac arrhythmia was also evaluated from Holter recording. The mean supraventricular and ventricular arrhythmias at baseline were 0.0815 % and 0.0065 %, respectively. After receiving ivabradine, one of the four dogs had higher supraventricular (from 0.26% at baseline to 1.34% at M3) and ventricular (from 0.009% at baseline to 0.015% at M3) arrhythmias while arrhythmias of the rest of the dogs did not change.

The result of time domain analysis of HRV is shown in Figure 4. In response to repeated oral dose of ivabradine, SDNN, SDANN, SDNN index, pNN50 and rMSSD when measured at M3 were significantly higher (54.5 %, 57.8 %, 53.8 %, 56.8 % and 77.1 %, respectively) when compared with baseline ($P < 0.05$). After treatment with ivabradine for 2 months (M2) and 3 months (M3), the NNA value was significantly higher than the value at baseline (13.9 % and 21.9 %, respectively) ($P<0.05$).

The result of frequency domain (PSD, power spectral density) analysis of HRV was shown in Figure 5. Dogs receiving ivabradine for 3 months had significant higher low frequency (104.7 %), high frequency (159.8 %) and total power (135.9 %) when compared with baseline ($P<0.05$), but no significant difference was found for the ratio of low frequency to high frequency at all time-points when compared with baseline.

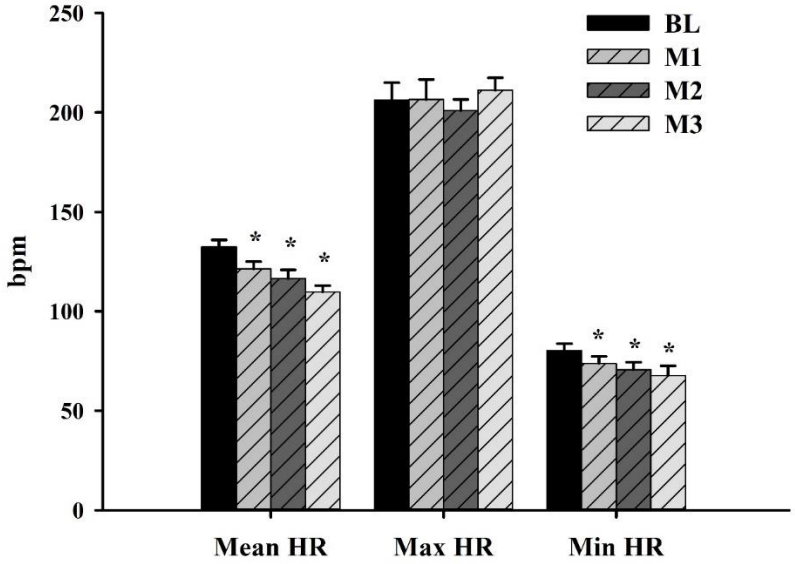

Figure 3 Histogram illustration of an average of 24-h Holter monitoring parameters including heart rate (mean HR), maximum instantaneous heart rate (Max HR), and minimum instantaneous HR (Min HR) of dogs with degenerative mitral valve disease obtained at baseline (BL) and after chronic administration of 1 mg/kg ivabradine orally twice a day (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks). *indicates $P < 0.05$ when compared with baseline, bpm = beat per minute

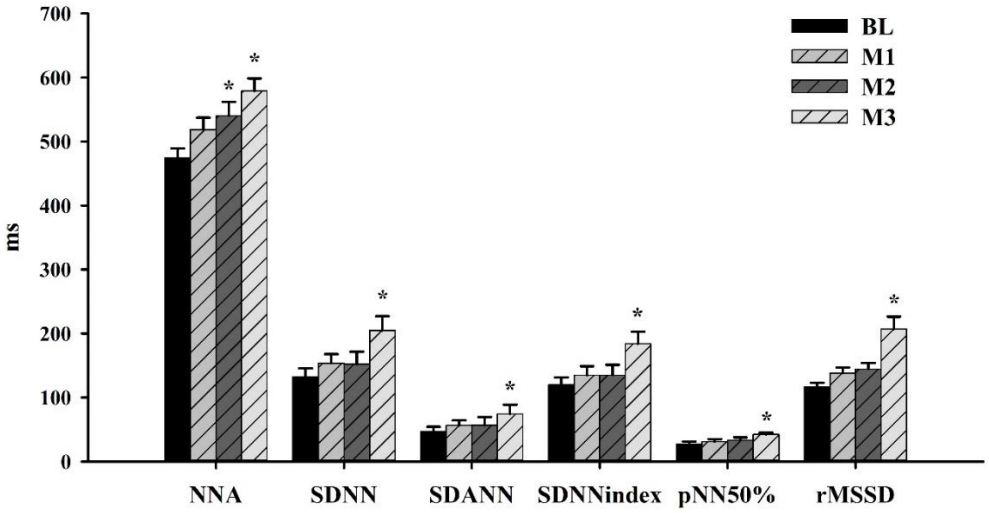

Figure 4 Histogram illustration of an average of time domain indices of heart rate variability including the mean NN intervals (NNA), standard deviation of all normal to normal RR intervals (SDNN), the standard deviation of 5-min mean RR intervals (SDANN), the mean of the standard deviation of all normal-to-normal RR intervals for all 5-min segments (SDNN index), the percentage of successive normal RR intervals exceeding 50 ms (pNN50) and the square root of the mean of the squares of the differences between successive normal to normal RR intervals (rMSSD) of dogs with degenerative mitral valve disease obtained at baseline (BL) and after chronic administration of 1 mg/kg ivabradine orally twice a day (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks). *indicates $P < 0.05$ when compared with baseline, PSD = power spectral density, ms^2 = millisecond square

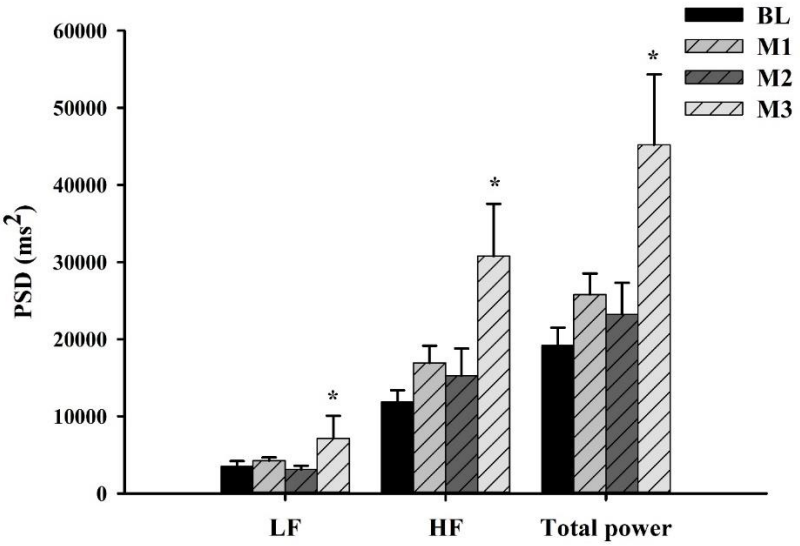

Figure 5 Histogram illustration of an average of frequency domain indices of heart rate variability including low frequency (LF), high frequency (HF), and total power of dogs with degenerative mitral valve disease obtained at baseline (BL) and after chronic administration of 1 mg/kg ivabradine orally twice a day (M1 = 4 weeks, M2 = 8 weeks, and M3 = 12 weeks). *indicates $P < 0.05$ when compared with baseline, PSD = power spectral density, ms^2 = millisecond square

Discussion

The important goal of this study was to assess the chronic effects of ivabradine on alteration of cardiac ANS activity in stage B2 DMVD dogs. ANS activity was estimated by evaluation of time- and frequency-domain parameters of HRV, because ANS activity is difficult to evaluate directly. Abnormal ANS input to the heart resulting in the decreased of HRV parameters (stein et al., 1994). The time-domain parameters consist of NNA, SDNN, SDANN, SDNN index, rMSSD and pNN50. The NNA is a mean of RR interval in the entire recording, increased NNA related to the decreased of HR (a reciprocal of RR interval). The SDNN reflects changes in sympathetic and parasympathetic activities whereas the SDANN and SDNN index reflect sympathetic and parasympathetic activities that are attributable to baroreceptor reflex (Calvert, 1998; Sztajzel, 2004). In this study, increased SDNN indicates the increase of sympathetic and parasympathetic activities while increased SDANN and SDNN index suggest the increase of baroreflex activity. In addition, SDNN, SDANN and SDNN index have been shown to be associated with LF (Calvert, 1998). The pNN50 and

rMSSD are associated with HF in which these indices are attributed to the effect of vagal activity (Calvert, 1998). In the present study, increased pNN50, rMSSD, and HF suggest the increase of vagal activity. The Total power (TP) is the sum of all spectral frequency bands in which it was increased in the present study; therefore, the overall cardiac autonomic regulation is improved (stein et al., 1994; Task Force of the European Society of Cardiology, 1996; Calvert, 1998; Sztajzel, 2004). The LF/ HF is the index of sympathetic and parasympathetic balance (i.e. sympatho-vagal balance). In the current study, the LF/ HF did not differ among time-points after treatment (M1, M2, and M3) and baseline while other HRV parameters are augmented. This discrepancy may be supported by Billman (2013), in which it was demonstrated that the LF/HF ratio does not accurately measure cardiac sympatho-vagal balance, since the ratio is rested upon several interrelated assumptions.

The present study also demonstrated that asymptomatic DMVD dogs have impaired cardiac ANS activities suggested by low values of both time- and frequency- domain parameters at baseline (i.e. SDNN, SDANN, SDNN index, pNN50, rMSSD, low frequency, high frequency and total power). This finding is consistent with previous studies of DMVD dogs (Fujii and Wakao, 2003; Rasmussen et al., 2012; Pirintr et al., 2017). In the present study, HRV increased gradually and a statistically significant increase was recorded at M3 after ivabradine treatment. To our knowledge, this is the first study showing the benefit of ivabradine to improve HRV in DMVD dogs. Similar findings have been reported previously in patients with non-ischemic dilated cardiomyopathy (Kurtuglu et al., 2014).

Because the impairment of sympathovagal balance (i.e. sympathetic over activation and/or parasympathetic withdrawal) is a hallmark of CHF, a drug that can improve HRV might be beneficial in clinical use. In addition, a lower HRV has been shown to be associated with poor cardiovascular outcome (Billman, 2011). Therefore, the increase in HRV after receiving ivabradine in the present study suggest the potential use of ivabradine in asymptomatic DMVD. The current study did not investigate the possible mechanisms responsible for the improvement of HRV by ivabradine; however, evidence from several studies suggests that it may be due to the lower HR (i.e. increase diastolic filling time) together with reverse remodeling (Kurtuglu et al., 2014; Sabbah et al., 2014).

A lower NNA (the reciprocal of a higher HR) is related to severity of DMVD; therefore, NNA can be used for evaluation of autonomic dysfunction (Rasmussen et al., 2012). In the present study, NNA was significantly higher after treatment with ivabradine. This result is similar to previous studies observed in DMVD and normal dogs (Colin et al., 2004) because ivabradine is a pure funny channel blocker that affects spontaneous diastolic depolarization at the sino-atrial node (Di Francesco and Camm, 2004). Several clinical trials in humans have demonstrated that ivabradine can lower HR and improve of cardiac function, and improve quality of life without negative inotropism (Fox et al., 2009; Swedberg et al., 2010).

The current study also showed that the minimum instantaneous HR decreased whereas the maximum instantaneous HR was unchanged after treatment with ivabradine. This change in HR did not induce bradycardia or any other arrhythmia. This is consistent with the finding of the current study that most of the dogs showed unchanged of the incidence of supraventricular and ventricular arrhythmias after receiving ivabradine. The effect of ivabradine on arrhythmia induction was unclear. Studies conducted in dogs with age-related AF and in dogs with vagal nerve stimulation showed that ivabradine did not increase the risk of AF in those dogs (Li et al., 2015; Uemura et al., 2017).

In addition to lowering HR, the current study in asymptomatic DMVD dogs demonstrated that systemic BP is decreased in response to chronic administration of ivabradine. The finding is contrast to our previous study in a similar group of dogs in which a single oral administration of 1 mg/kg ivabradine did not alter systemic BP (Pirintr et al., 2018). A decrease in BP may be caused by lower HR, because BP is determined by HR, stroke volume and total peripheral resistance. Furthermore, MVO_2 estimated by rate-pressure product is reduced, which helps to reduce the workload of the heart and improve cardiac efficiency (Suga, 1979).

In conclusion, both the time- and frequency-domain of HRV indices were low in DMVD dogs, suggesting parasympathetic withdrawal and/or sympathetic activation. Dogs with mild DMVD receiving long-term treatment with ivabradine (1 mg/kg, twice daily, orally) had increased cardiac autonomic modulation, as suggested by both time- and frequency-domain indices. Long-term administration of ivabradine lowered HR and BP without increasing cardiac arrhythmia in DMVD dogs. In addition, a decrease in MVO_2 suggested the improvement of cardiac efficiency. Therefore, ivabradine may be useful for maintaining normal ANS activity in dogs with asymptomatic DMVD. Furthermore, long-term treatment with ivabradine improves systolic and diastolic function of the left ventricle, suggesting that using ivabradine in a clinical setting is beneficial.

***Potential limitations*:** There are a couple limitations in the present study; therefore, the result must be interpreted with caution. First, the study was performed in a small sample size due to the availability of subjects. The lack of statistically significant differences in some parameters between ivabradine and baseline may be influenced by this small sample size. However, the small sample size did not affect the overall outcome of the study. In addition, the study supports the use of the 3R concept (i.e. replacement, reduction, and refinement) by using fewer animals to achieve the objectives of the study. Second, the plasma concentrations of ivabradine in DMVD dogs were not performed. The data of plasma ivabradine concentration may provide more detail of the relationship between drug concentration and its effect; however, it is not a major goal of the study. The pharmacokinetic of ivabradine in DMVD dogs has not been investigated; therefore, further investigation of

ivabradine should be conducted in various stages of DMVD dogs.

Conflict of Interest: The authors declare that they have no conflict of interest.

Acknowledgements

This study was supported by the Thailand Research Fund through the Royal Golden Jubilee Ph.D. Program (Grant No. PHD/0161/2557) to PP and AK and Thailand Research Fund and Chulalongkorn University (Grant No. RSA6080020 and RES6105131006RE1). The laboratory of Dr. AK is also supported by the Special Task Force for Activating Research (GSTAR 59-002-31-002).

References

Billman GE 2011. Heart rate variability—a historical perspective. Front Physiol. 2: 86.

Billman GE 2013. The LF/HF ratio does to accurately measure cardiac sympatho-vagal balance. Front Physiol. 4: 1-5.

Bucchi A, Barbuti A, Baruscotti M and DiFrancesco D 2007. Heart rate reduction via selective 'funny' channel blockers. Curr Opin Pharmacol. 7(2): 208-213.

Calvert CA 1998. Heart rate variability. Vet. Clin. North Am. Small Anim Pract. 28(6): 1409-1427.

Chompoosan C, Buranakarl C, Chaiyabutr N and Chansaisakorn W 2014. Decreased sympathetic tone after short-term treatment with enalapril in dogs with mild chronic mitral valve disease. Res Vet Sci. 96(2):347-54.

Cober RE, Schober KE, Buffington TC, Li X, Riesen SC and Bonagura JD 2011. Pharmacodynamic effects of ivabradine, a negative chronotropic agent, in healthy cats. J Vet Cardiol. 13(4): 231-242.

Colin P, Ghaleb B, Monnet X, Hittinger L and Berdeaux A 2004. Effect of graded heart rate reduction with ivabradine on myocardial oxygen consumption and diastolic time in exercising dogs. J Pharmacol Exp Ther. 308(1): 236-240.

De Jong MJ and Randall DC 2005. Heart rate variability analysis in the assessment of autonomic function in heart failure. J Cardiovasc Nurs. 20(3): 186-195.

Di Francesco D and Camm AJ 2004. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. Drugs. 64(16): 1757-1765.

FDA 2015. "Subject: FDA approves Corlanor to treat heart failure" (online). Available: www.fda.gov.

Fox K, Ford I, Steg PG, Tendera M, Robertson M and Ferrari R 2009. BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J. 30(19): 2337-2345.

Fujii Y and Wakao Y 2003. Spectral analysis of heart rate variability in dogs with mild mitral regurgitation. Am J Vet Res. 64(1): 145-148.

Karcz M, Chojnowska L, Zareba W and Ruzyllo W 2003. Prognostic significance of heart rate variability in dilated cardiomyopathy. Int J Cardiol. 87(1): 75-81.

Kijtawornrat A, Komolvanich S, Saengklub N, Pirintr P, Boonpala P and Buranakarl C. 2017. Long-term effect of sildenafil on echocardiographic parameters in dogs with asymptomatic myxomatous mitral valve degeneration. J Vet Med Sci. 79(4): 788–794.

Kurtuglu E, Balta S, Karakus Y, Yasar E, Cuglan B, Kaplan O and Gozubuyuk G 2014. Ivabradine improves heart rate variability in patients with nonischemic dilated cardiomyopathy. Arq Bras Cardiol. 103(4): 308-314.

Li YD, Ji YT, Zhou XH, Jiang T, Hong YF, Li JX, Xing Q, Xiong J, Yusufuaji Y and Tang BP 2015. Effects of ivabradine on cardiac electrophysiology in dogs with age-related atrial fibrillation. Med Sci Monit. 21: 1414-1420.

National Research Council 2011. Guide for the Care and Use of Laboratory Animals: 8th ed. Washington, DC: The National Academies Press. 220pp.

Nordlander R, Pehrsson SK and Aström H 1989. The reliability of rate-pressure product as an index of myocardial oxygen consumption in atrial synchronized versus fixed rate ventricular pacing. Pacing Clin Electrophysiol. 12(6): 917-921.

Oyama MA 2009. Neurohormonal activation in canine degenerative mitral valve disease: implications on pathophysiology and treatment. J Small Anim Pract. 50(Suppl 1): 3-11.

Pirintr P, Chansaisakorn W, Trisiriroj M, Kalandakanond-Thongsong S and Buranakarl C 2012. Heart rate variability and plasma norepinephrine concentration in diabetic dogs at rest. Vet Res Commun. 36(4): 207-214.

Pirintr P, Saengklub N, Limprasutr V, Sawangkoon S and Kijtawornrat A 2017. Sildenafil improves heart rate variability in dogs with asymptomatic myxomatous mitral valve degeneration. J Vet Med Sci. 79(9): 1480-1488.

Pirintr P, Limprasutr V, Saengklub N, Pavinadol P, Yapao N, Limvanicharat N, Kuecharoen H and Kijtawornrat A 2018. Acute effect of ivabradine on heart rate and myocardial oxygen consumption in dogs with asymptomatic mitral valve degeneration. Exp Anim. Doi: 10.1538/expanim.18-0030.

Rasmussen CE, Falk T, Zois NE, Moesgaard SG, Haggstrom J, Pedersen HD, Ablad B, Nilsen HY and Olsen LH 2012. Heart rate, heart rate variability, and arrhythmias in dogs with myxomatous mitral valve disease. J Vet Intern Med. 26(1): 76-84.

Rosano GMC, Vitale C, Spoletini I and Volterrani M 2014. Clinical utility of ivabradine in cardiovascular disease management: current status. Clin cardiol. 5: 183-187.

Sabbah HN, Gupta RC, Kohli S, Wang M, Zhang K and Rastogi S 2014. Heart rate reduction with ivabradine improves left ventricular function and reverses multiple pathological maladaptations in

dogs with chronic heart failure. ESC Heart Fail. 1(2): 94-102.

Stein PK, Bosner MS, Kleiger RE and Conger BM 1994. Heart rate variability: A measure of cardiac autonomic tone. Am Heart J. 127(5): 1376-1381.

Suga H 1979. Total mechanical energy of a ventricle model and cardiac oxygen consumption. Am J Physiol. 236(3): H498-H505.

Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L and Investigators S 2010. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. Lancet. 376(9744): 875-885.

Sztajzel J 2004. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly. 14: 514-522.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 17(3): 354-381.

Uemura K, Inagaki M, Zheng C, Kawada T, Li M, Fukumitsu M and Sugimachi M 2017. Acute ivabradine treatment reduces heart rate without increasing atrial fibrillation inducibility irrespective of underlying vagal activity in dogs. Heart Vessels. 32(4): 484-494.

Vachon C, Belanger MC and Burns PM 2014. Evaluation of oscillometric and Doppler ultrasonic devices for blood pressure measurements in anesthetized and conscious dogs. Res Vet Sci. 97(1): 111-117.

บทคัดย่อ

ผลของการให้ยาไอวาบราดีนแบบรับประทานที่ให้แบบต่อเนื่องต่อความแปรปรวนในอัตราการเต้นของหัวใจในสุนัขที่ภาวะลิ้นหัวใจไมตรัลเสื่อมแบบไม่แสดงอาการ

ประภาวดี ไพรินทร์[1] นรรฆวี แสงกลับ[2] วุฒิพร ลิ้มประสูตร[3] อนุศักดิ์ กิจถาวรรัตน์[1*]

โรคลิ้นหัวใจไมตรัลเสื่อมเป็นโรคหัวใจที่เกิดขึ้นภายหลังกำเนิดและพบมากในสุนัขสูงอายุ ซึ่งนำไปสู่ความผิดปกติของระบบประสาทอัตโนวัติที่ควบคุมการทำงานของหัวใจ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลของการให้ยาไอวาบราดีนในรูปแบบรับประทานที่ให้แบบต่อเนื่อง ต่ออัตราการเต้นของหัวใจ ความดันโลหิตร่างกาย ปริมาณความต้องการใช้ออกซิเจนของกล้ามเนื้อหัวใจ และความแปรปรวนในอัตราการเต้นของหัวใจในสุนัขที่ภาวะลิ้นหัวใจไมตรัลเสื่อมแบบไม่แสดงอาการระยะ B2 โดยใช้สุนัขพันธุ์บีเกิ้ลที่มีภาวะลิ้นหัวใจไมตรัลเสื่อมแบบไม่แสดงอาการที่เกิดขึ้นเองโดยธรรมชาติในระยะ B2 จำนวน 4 ตัว มาติดเครื่องบันทึกคลื่นไฟฟ้าหัวใจแบบต่อเนื่อง 24 ชั่วโมง เพื่อวัดคลื่นไฟฟ้าหัวใจ และนำไปคำนวณค่าความแปรปรวนในอัตราการเต้นของหัวใจ ทำการวัดความดันโลหิตและอัตราการเต้นของหัวใจเพื่อนำไปคำนวณค่า rate-pressure product ซึ่งใช้ในการคำนวณค่าปริมาณความต้องการใช้ออกซิเจนของกล้ามเนื้อหัวใจทางอ้อม โดยสุนัขแต่ละตัวได้รับยาไอวาบราดีนในขนาด 1.0 มก.ต่อกก. วันละ 2 ครั้ง เช้า-เย็น เป็นเวลา 3 เดือน และทำการเก็บข้อมูลก่อนได้รับยาและหลังการป้อนยาทุก ๆ 4 สัปดาห์ เป็นเวลา 12 สัปดาห์ (M1 บันทึกที่ 4 สัปดาห์ M2 บันทึกที่ 8 สัปดาห์ และ M3 บันทึกที่ 12 สัปดาห์) ผลการทดลองพบว่าการได้รับยาไอวาบราดีนแบบต่อเนื่องมีผลในการลดอัตราการเต้นของหัวใจ ความดันโลหิต และปริมาณความต้องการใช้ออกซิเจนของกล้ามเนื้อหัวใจอย่างมีนัยสำคัญ ($P < 0.05$) โดยไม่พบผลข้างเคียงที่ไม่พึงประสงค์ การบันทึกที่ 3 เดือนหลังจากที่สุนัขได้รับยาไอวาบราดีนพบว่าค่าความแปรปรวนในอัตราการเต้นของหัวใจวิเคราะห์ตามช่วงเวลาและตามความถี่มีค่าเพิ่มขึ้นอย่างมีนัยสำคัญ ($P < 0.05$) เมื่อเทียบกับช่วงก่อนได้รับยา จากผลการทดลองจึงสรุปได้ว่ายาไอวาบราดีนแบบรับประทานในขนาด 1.0 มก.ต่อกก. วันละ 2 ครั้ง เช้า-เย็น สามารถลดอัตราการเต้นของหัวใจ ความดันโลหิตร่างกาย ปริมาณความต้องการใช้ออกซิเจนของกล้ามเนื้อหัวใจ และช่วยฟื้นฟูการทำงานของระบบประสาทอัตโนวัติที่ควบคุมการทำงานหัวใจในสุนัขที่มีภาวะลิ้นหัวใจไมตรัลเสื่อมแบบไม่แสดงอาการในระยะ B2 ได้ จึงกล่าวได้ว่ายาไอวาบราดีนมีศักยภาพในการใช้ลดอัตราการเต้นของหัวใจ และช่วยฟื้นฟูการทำงานของระบบประสาทอัตโนวัติที่ควบคุมการทำงานหัวใจในสุนัขที่มีภาวะลิ้นหัวใจไมตรัลเสื่อมแบบไม่แสดงอาการในระยะ B2

คำสำคัญ: สุนัข ความแปรปรวนในอัตราการเต้นของหัวใจ ไอวาบราดีน ภาวะลิ้นหัวใจไมตรัลเสื่อม

[1]ภาควิชาสรีรวิทยา คณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย 39 ถนนอังรีดูนังต์ แขวงวังใหม่ เขตปทุมวัน กรุงเทพมหานคร 10330
[2]ภาควิชาสรีรวิทยา คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล 447 ถนนศรีอยุธยา เขตราชเทวี กรุงเทพมหานคร 10400
[3]ภาควิชาเภสัชวิทยาและสรีรวิทยา คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย 254 ถนนพญาไท เขตปทุมวัน กรุงเทพมหานคร 10330
****ผู้รับผิดชอบบทความ** E-mail: anusak.k@chula.ac.th*