Original Article

Effects of coenzyme Q10 supplementation on cardiac troponin I level, heart rate variability, and echocardiographic profiles in canine with myxomatous degenerative mitral valve disease: a pilot study

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Abstract

The clinical benefits of Coenzyme Q10 (CoQ10) have been well documented in heart failure patients. In veterinary medicine, however, the clinical benefits of CoQ10 have not been well established in dogs with heart diseases. This study aimed to determine the effects of CoQ10 supplementation on 1) preventing myocardial injury 2) cardiac function 3) autonomic balance in dogs with myxomatous degenerative mitral valve disease (MMVD). Thirteen dogs with MMVD at ACVIM stage C were recruited in this study. Dogs were further divided into group I (Body weight [BW] < 6 kg.; n = 7) and group II (BW ≥ 6 kg.; n = 6). Cardiac troponin I (cTnI), echocardiographic examination, and 2 hours of Holter recording were performed on Day 0 and after receiving CoQ10 at 100 mg/dog twice daily for 28 days. CoQ10 caused a reduction of cTnI level in 71% of the dogs. Median cTnI tended to cause tended to decline but not significantly. Systolic function [i.e. fractional shortening (FS) and ejection fraction (EF)] increased significantly by 8 % and 9% ($P < 0.05$), respectively in group I after CoQ10 supplementation. Other echocardiographic parameters were not altered in either group. HRV analysis revealed no change in autonomic function and balance. cTnI negatively correlated with FS ($P < 0.01$) and positively correlated with LF/HF ratio ($P < 0.05$). In conclusion, this study demonstrated the clinical benefits of CoQ10 supplementation in dogs with MMVD. CoQ10 improves cardiac function in small dogs with MMVD. Finally, supplementation of CoQ10 in dogs should be based on body weight.

Keywords: Cardiac troponin I, CoQ10, Dog, Heart rate variability, Myxomatous degenerative mitral valve disease

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Introduction

Coenzyme Q10 (CoQ10) has been reported to be of benefit and is recommended as a nutraceutical in heart failure (HF) patients. However, the clinical efficacy of CoQ10 in HF patients remains controversial since several studies have reported no advantage of CoQ10 over placebos (DiNicolantonio et al., 2015). Likewise, in veterinary medicine there is also limited information regarding the clinical benefits of CoQ10 in dogs. In fact, only one study has reported the role of CoQ10 in dogs with experimental induced congestive HF (Harker-Murray et al., 2000). Still, CoQ10 is recommended by some review literature extrapolating from human medicine for use in dogs with heart disease (Sagols and Priymenko, 2011).

CoQ10 or ubiquinone is a component in the oxidative phosphorylation process in the mitochondrial membrane which enhances ATP production in the cells. It also possesses an anti-oxidative effect which reduces free radicals in the cells and promotes cell membrane stabilization (Greenberg and Frishman, 1990; Littarru and Tiano, 2007). In addition, other benefits of CoQ10 on cardiovascular systems have also been mentioned such as improvement of endothelial function, promoting vasodilatory effects and stabilization of some cellular proteins, (Kumar et al, 2009). CoQ10 supplementation has also been shown to attenuate the hypertrophic response in dogs with experimentally induced congestive heart failure (Harker-Murray et al., 2000).

Myxomatous degenerative mitral valve disease (MMVD) is the most common heart disease found in small breed dogs with a high prevalence (ranging between 3.5% and 69.7%) (Detweiler and Patterson, 1965; Whitney, 1974; Thrusfield, 1985). Affected dogs usually present to the veterinarian with signs of left-sided congestive heart failure. As a result of inadequate cardiac output, the body begins to preserve cardiac function by enhancing sympathetic tone and activating renin-angiotensin-aldosterone system (RAAS) (Hillege et al., 2000; Freeman et al., 2005). However, these compensatory effects increase the workload on the heart by increasing energy consumption and utilization which promotes oxidative stress and damage to cardiomyocytes. Consequently, myocardial injury occurs and leads to cardiac remodeling with a further reduction in the heart function. Thus, current medication therapies of MMVD including angiotensin-converting enzyme inhibitors (ACEi), diuretics, and positive inotropes aim to attenuate the progression of the heart disease by reducing heart workload, alters the neurohormonal systems and reduces oxidative stress. Recently, neutraceuticals such as CoQ10 have gained attention as an adjunctive therapy in animals and humans with heart disease.

The clinical benefits of CoQ10 in a dog with MMVD have not yet been investigated. Besides its clinical benefits in heart disease, a study in humans demonstrated that CoQ10 augmented autonomic nervous system (ANS) activity based on heart rate availability (HRV) analysis with some benefits in obese or hyperlipidemia patients (Zheng and Moritani, 2008). Currently, the effect of CoQ10 on the ANS in dogs with heart disease has not been studied. The objective of this study was to determine the clinical benefits of CoQ10 on cardiac and ANS function and its cardio-protective action in MMVD dogs.

Materials and Methods

The protocol of this study was approved by the Institutional Animal Care and Use Committee, Faculty of Veterinary Science, Chulalongkorn University. Approval and consent form was obtained from the owners of the dogs enrolled in the study.

Animals: Thirteen dogs were presented at the Cardiology Unit, Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand, for investigation of cardiac disease. All dogs presented with a history of coughing, exercise intolerance and/or syncope with murmur heart sound were included in this study. Congestive HF was determined by the presence of pulmonary edema from the thoracic radiography. All dogs were diagnosed with MMVD by echocardiography and categorized in stage C according to the American College of Veterinary Internal Medicine (ACVIM) (Atkins et al., 2009). All dogs were prescribed a combination of enalapril (0.25-0.5 mg/kg) twice a day and furosemide (1-4 mg/kg/day) for at least 2 months duration. No other cardiovascular drugs or antioxidant substrates were prescribed prior to the study.

Study design: A cross-sectional study with before-and-after design experiment was used in the current research. The effect of CoQ10 was examined in dogs before and after receiving CoQ10 (100 mg soft gels, Trunature®, Costco, Seattle, WA; U.S.A.) at a dosage of 100 mg/dog (Dove, 2001) twice daily for 28 days. Because the recommended dose (Dove, 2001) of CoQ10 was given per animal, the dogs were further divided into 2 groups based on their body weight; group I: body weight less than 6 (n = 7) and group II: body weight equal to or more than 6 kg (n = 6) to observe whether there is a dose dependent effect of CoQ10. At the day of the experimental study, all dogs were subjected to blood collection, echocardiographic examination and ECG lead attachment for Holter monitoring study.

Whole blood and serum analysis: Five ml of blood were collected from the cephalic vein of the dogs and kept in EDTA and/or heparinized tube for measurement of the complete blood count (red blood cells count; RBC, hemoglobin concentration; Hb, hematocrit; Hct, platelet count and white blood cells count; WBC), and biochemical profiles (serum glutamate pyruvate transaminase; SGPT, alkaline phosphatase; ALP, blood urea nitrogen; BUN and creatinine; Cr, respectively). Evaluation of the serum cardiac troponin I (cTnI) was performed using the Quantitative immunochromatography technique (QuickSens 100®, Labotron). The antibody against the C5 domain of human cardiac TnI was used in the assay. Since TnI is highly conserved among species, this assay

is valid for use in dogs (Oyama and Sission, 2004). The detection range of the assay was 0-400 ng/ml.

Ambulatory electrocardiographic monitoring: A Holter device (Digital walk FM-180; Fukuda Denshi, Co Ltd. Tokyo, Japan) with 7 electrodes was placed on the dogs for two hours according to the precordial lead placement technique (Pereira et al., 2008) to evaluate the heart rate variability (HRV) as described previously (Chompoosan et al., 2004). The data was analyzed with the SCM-510 software for the HRV in both frequency and time domains. The data was averaged from three consecutive 10 mins based on normal R wave for more than 85% consecutively. HRV parameters were measured at the number of samples 512s. For the frequency domain, high frequency (HF) and low frequency (LF) values, as well as LF/HF ratio, were analyzed. The time domain analysis was analyzed including a standard deviation of total RR interval (SDNN), average of 5-minutes RR interval standard deviation (SDNN index), standard deviation of 5-minutes RR interval average (SDANN), percentage of pairs of adjacent NN intervals differing by more than 50 millisecond (pNN50), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD). The vasovagal tone index (VVTI) could be calculated by ln(SDNN) (Pereira et al., 2008; Oliveira et al., 2012).

Echocardiography: Echocardiography was performed by one experienced echocardiographer. A right parasternal long axis view was performed to examine the overview of the heart chamber and the mitral valve structure in B-mode. Abnormalities of the mitral valve leaflets were confirmed in B-mode including thickening, prolapse or both. In addition, the mitral regurgitation was assessed by the Doppler-color flow mode. Moreover, M-mode was used to obtain the left atrial diameter (LA), aortic root diameter (AO) and the LA:AO ratio. For the right parasternal short axis view, M-mode was performed to evaluate the interventricular septum (IVS) during systole and diastole, left ventricular internal dimension (LVID) during systole and diastole, left ventricular posterior free wall (LVPW) during systole and diastole and the percentage of fractional shortening (FS) (Boon, 2011). All the M-mode echocardiographic values were calculated according to the allometric equations of Cornell et al (2004). End diastolic volume index (EDVI), end systolic volume index (ESVI) and, ejection fraction (EF) were calculated by the veterinary Teichholz method formula (de Madron et al., 2016).

Statistical analysis: Statistical analyses were done using commercially available software. Results of cTnI concentration were expressed as a median with interquartile range. The Shapiro-Wilk normality test was used to test for the Gaussian distribution. A value of $P < 0.05$ was considered significant. Results of echocardiographic parameters and HRV parameters were expressed as a mean $\pm$ standard error of the mean (SEM). The effects of CoQ10 on serum cTnI, HRV and echocardiographic parameters were compared before and after receiving CoQ10 using Wilcoxon match-paired signed rank test and statistical significance was defined by $P < 0.05$. The weight dependent effect of CoQ10 on echocardiographic parameters and HRV between group I and group II were tested by two-way ANOVA with Bonferroni post-test. Pearson's correlation coefficient (r) was used to determine the relationship of cTnI, LF/HF ratio and FS with a significant difference considered at $P < 0.05$.

Results

Population characteristics: General characteristics of the study population are shown in Table 1. Thirteen DMVD dogs at the ACVIM stage C were recruited in the study with nine males and four females. The average age of the dogs was slightly higher in group II (≥ 6 kg) compared with group I (< 6 kg). Various breeds were included in the study which were mostly small breed dogs. The average weight of the group II was higher than in group I. After CoQ10 supplementation, the weight in both groups had not changed significantly (Table 2).

Complete blood count revealed that none of the parameters was significantly changed before and after 28 days of receiving CoQ10 with a fall in normal reference range (data not shown).

Table 1 General characteristics of the study population

Variables	Total dogs (n=13)	Group I Dogs (<6 kg.) (n= 7)	Group II Dogs (≥ 6kg.) (n=6)
Age (years)	10.9±0.90	9.71± 1.49	12.17± 0.65
Weight (kg)	6.87± 1.00	4.65± 0.57	9.46± 1.49
Breeds (number)			
Poodle	5	2	3
Miniature Pinscher	3	2	1
Shih Tzu	2	2	
Pug	1	0	1
Chihuahua	1	1	0
American cocker spaniel	1	0	1
Gender (number)			
M/Mc/F/Fs	6/3/3/1	3/2/1/1	3/1/2/0

Data is presented as mean ± SEM. M male, Mc castrated male, F female, Fs, Spayed female.

Table 2 Weight and cTnI concentration before and after receiving CoQ10 in study population.

Variables	Total dogs (n=13)		Group I Dogs (<6 kg.) (n= 7)		Group II Dogs (≥ 6kg.) (n=6)	
CoQ10	Before	After	Before	After	Before	After
Weight (kg)	6.87± 1.00	6.78± 0.96	4.65± 0.57	4.69± 0.6	9.46± 1.49	9.230± 1.42
cTnI (ng/ml)	0.22 (0.02-1.17)	0.09 (0.02-2.09)	0.28 (0.02-1.38)	0.21 (0.02-3.09)	0.22 (0.01-2.48)	0.02 (0.02-1.58)

Data is presented as mean ± SEM for weight and median with interquartile range for cTnI concentration.

Plasma cTnI concentration: Results of plasma cTnI concentrations are shown in Figure 1 and Table 2. In the beginning, 64% of dogs had elevated plasma cTnI ranging from 0.13 - 4.73 ng/mL. Whereas, 27% of dogs had an undetectable cTnI level. 71.4% of dogs with the elevated cTnI level before prescription of CoQ10 had a lower cTnI level (range; 0.02 - 2.89 ng/mL) after 28 days of receiving CoQ10 (Figure 1A). 28.6% of dogs had a higher cTnI level (range; 2.09-6.1 ng/mL) after prescribed CoQ10. There were two dogs with plasma cTnI above the 75% percentile in pre-treatment dogs. Likewise, two dogs had plasma cTnI above the 75% percentile in post-treatment dogs. The scattered dot plot with a median of plasma cTnI concentration in group I and group II dogs is shown in Figure 1B and 1C, respectively. There was no difference in median cTnI level in either group of dogs. Although these results are not statistically significant, plasma cTnI concentration tended to decline in the treated dogs.

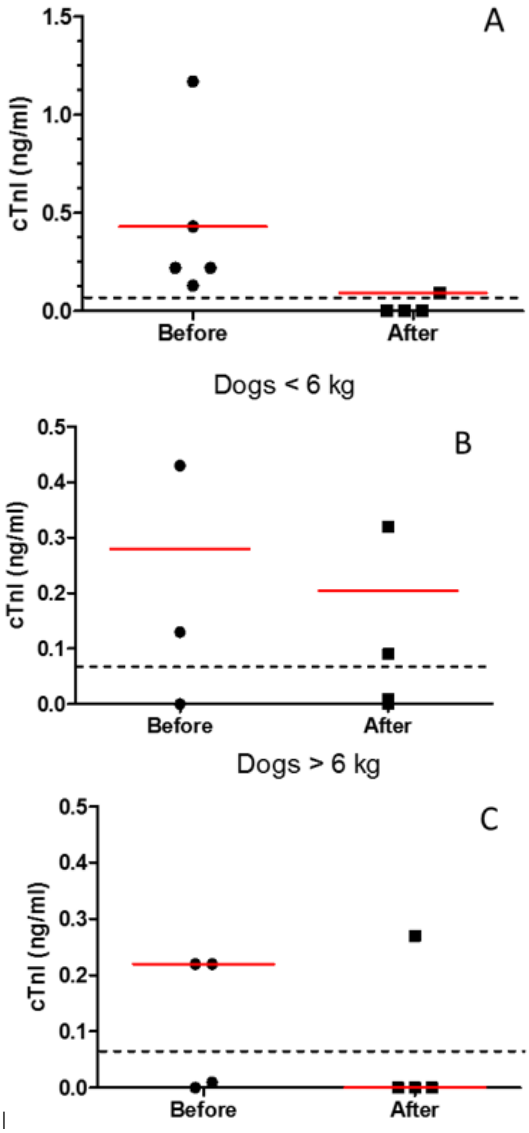

Figure 1 Scatter dot plot show plasma concentrations of cardiac troponin-I (cTnI) before and after receiving CoQ10 in dogs with MMVD. A) All dogs, B) dogs weight less than six kilogram, C) dogs weight equal or over six kilogram. The median value is shown as the red horizontal line.

Table 3 Echocardiographic values from 13 dogs with DMVD before and after CoQ10 supplementation.

Parameters	Group I: Dogs < 6 kg (n=7)					Group II: Dogs ≥ 6 kg (n=6)				
	Before		After		p-value	Before		After		p-value
	Mean	SEM	Mean	SEM		Mean	SEM	Mean	SEM	
IVSd	0.51	0.03	0.42	0.05	0.12	0.48	0.03	0.39	0.03	0.22
LVIDd	1.48	0.18	1.77	0.17	0.43	1.85	0.22	1.25	0.31	0.05
LVPWd	0.53	0.07	0.48	0.09	0.73	0.61	0.05	0.68	0.24	0.82
IVSs	0.99	0.11	0.91	0.09	0.47	0.70	0.07	0.54	0.08	0.05
LVIDs	0.81	0.09	0.77	0.08	0.94	0.99	0.23	0.77	0.21	0.25
LVPWs	0.80	0.05	0.81	0.08	0.89	0.69	0.33	0.75	0.08	0.71
LA	1.18	0.11	0.99	0.09	0.24	1.11	0.17	0.70	0.10	0.09
AO	0.71	0.03	0.73	0.07	0.94	0.74	0.07	0.66	0.07	0.68
LA/AO	1.66	0.16	1.35	0.24	0.54	1.60	0.29	1.16	0.16	0.38
FS	44.68	3.15	56.49	2.89	<0.05*	46.48	5.75	38.40	3.36	0.20
EDVI	3.93	0.93	5.59	1.33	0.56	7.18	1.75	3.57	2.15	0.12
EVSI	0.67	0.11	0.59	0.13	0.68	1.57	0.88	0.89	0.61	0.25
EF	80.07	4.8	87.44	2.97	<0.05*	82.86	5.01	76.31	4.36	0.37

Results listed as mean (± SEM) for echocardiographic measurements (in cm.). LVIDd, left ventricular internal diastolic dimension; Ao, aorta; LVIDs, left ventricular internal systolic dimension; FS, fractional shortening; LA, left atrium; IVSd, interventricular septum end-diastolic thickness; LVPWd, left ventricular posterior wall end-diastolic thickness; EDVI, end diastolic volume index; EVSI, end systolic volume index; EF, ejection fraction. *P < 0.05 versus before receiving CoQ10.

Table 4 HRV parameters from 13 dogs with DMVD before and after CoQ10 supplementation.

Parameters	Group I: Dogs < 6 kg (n=7)					Group II: Dogs ≥ 6 kg (n=6)				
	Before		After		p-value	Before		After		p-value
	Mean	SEM	Mean	SEM		Mean	SEM	Mean	SEM	
HR (bpm)	117.90	5.66	120.9	7.99	0.69	114.5	4.90	118.2	8.02	0.77
LF power (msec)²	2300	712	1926	1458	0.57	1029	228	1315	163	0.21
HF power (msec)²	5034	1623	4196	1488	0.57	2206	1131	3132	1479	0.09
LF/HF	0.67	0.19	0.70	0.17	0.68	0.99	0.22	1.00	0.4	0.56
Total power (msec)²	12093	2800	8569.97	1951.52	0.10	5604	1866	8578	2953	0.09
SDANN (msec)	46.81	8.08	30.88	4.12	0.07	47.57	15.84	45.88	13.75	0.96
SDNN index (msec)	104.21	12.14	92.29	12.94	0.38	71.08	11.65	86.29	11.16	0.05
pNN50 (%)	43.59	7.42	32.78	7.89	0.29	20.79	6.78	26.45	4.98	0.29
RMSSD (msec)	105.20	11.93	93.69	12.64	0.37	73.26	12.34	88.51	11.94	0.06
Mean NN (msec)	530.68	26.66	495.04	33.20	0.34	491.17	15.39	492.25	27.42	0.97
VVTi	4.85	0.10	4.67	0.14	0.22	4.83	0.12	4.90	0.23	0.80

Results listed as mean (± SEM) for the HRV parameters; HR, Heart rate (beats per minute); HF, high frequency; LF, low frequency value; LF/HF, low frequency to high frequency ratio; SDNN, standard deviation of total RR interval average of 5-minutes; SDNN index, RR interval standard deviation; SDANN, standard deviation of 5-minutes RR interval average; pNN50, percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; *P < 0.05 versus before receiving CoQ10.

Echocardiographic study: Echocardiographic data from the group I and group II dogs is presented in Table 3. There was no difference in the mean of IVSd, LVIDd, LVPWd, IVSs, LVIDs, LVPWs, and LA/AO between before and after receiving CoQ10. However, both systolic function parameters (i.e. FS and EF) were significantly increased ($P < 0.05$) in group I dogs after oral administration of CoQ10 for 28 days. LVIDd and IVSs of group II dogs tended to decrease with a P-value equal to 0.05.

Heart rate variability analysis: The time-domain and frequency-domain parameters of HRV are shown in Table 4. There was no significant difference in heart rate before and after receiving CoQ10 in either group (Table 4). None of the time-domain parameters (i.e., SDANN, SDNN index, PNN50, RMSSD, Mean NN, and VVTi) was different between before and after receiving CoQ10 in either group. Notably, SDNN index tended to increase in group II with a P-value equal to 0.05. For the frequency-domain analysis, there were no significant differences in the HF power, LF power, and LF/HF between before and after receiving CoQ10. Total power also showed no significant difference between groups.

Correlation of cTnI, HRV, and echocardiographic values: Pearson correlation of cTnI, echocardiographic values, and HRV parameters (Table 5) revealed significant positive correlation between cTnI and LF/HF ratio ($r = 0.46$, $P = 0.03$, 95% CI 0.03 to 0.57, $n = 26$) and negative correlation between cTnI and FS ($r = -0.61$, $P = 0.0097$, 95% CI -11.41 to -1.86, $n = 26$). Meanwhile, FS has a tendency to negatively correlate with LF/HF ratio ($r = -0.55$, $P = 0.06$, 95% CI -0.08 to 0.002).

Table 5 Regression analysis of cTnI, Echocardiographic values, and HRV parameters.

Parameters	cTnI (ng/ml)	FS (%)	LF/HF	VVti
cTnI (ng/ml)		r = -0.61, p = 0.0097*	r = 0.46, p = 0.03*	r = -0.11, p = 0.61
FS (%)			r = -0.55, p = 0.06	r = 0.14, p = 0.52
LA/AO	r = -0.05, p = 0.83	r = 0.28, p = 0.20	r = -0.06, p = 0.77	r = -.019, p = 0.40
LVIDd/N (cm/kg)	r = -0,12, p = 0.59	r = - 0.19, p = 0.36	r = 0.20, p = 0.38	r = 0.10, p = 0.64

Data is presented as correlation coefficient (r) with p-value; *P<0.05.

Discussion

In humans, a number of trials with CoQ10 supplementation in heart failure patients demonstrated an improvement in cardiac function including EF and cardiac output (DiNicolantonio et al., 2015). To the best of the author's knowledge, this is the first veterinary clinical trial with an uncontrolled study to investigate the effects of CoQ10 supplementation in ACVIM stage C dogs with MMVD. Our results reveal that the 28 days of CoQ10 supplementation improved systolic function in small to middle-sized MMVD dogs.

CoQ10 supplementation to the MMVD dogs in the current study was in a soft-gel preparation. A previous study on bioavailability assessment of oral coenzyme Q10 formulations in dogs shown that soft-gel formulation is superior to regular power-filled formulations in regard to the bioavailability of the drug (Zaghloul et al., 2002).

The increased systolic function found in our study after MMVD dogs receiving CoQ10 was consistent with previous findings in several studies in humans (Lampertico and Comis, 1993; Langsjoen et al., 1997; Soongswang et al., 2005). By contrast, the only study in dogs experimentally induced CHF showed that at 4 weeks, none of the systolic function parameters (i.e. LVPSP, +dP/dt, and EF) in CoQ10 treated group was significantly different from the control although those parameters showed a tendency to increase. This may be due to the limitation in the number of animals in that study (n=6) and the difference in method to obtain parameters (in vivo catheterization). In the present study, we used FS and EF from echocardiography as a systolic function parameter. The increased systolic function can be explained by the fact that CoQ10 is a factor required during ATP production in mitochondria. Thus, CoQ10 supplementation may improve ATP availability for cardiac muscle contraction. The previous report showed that severity of CHF was found to be associated with a low level of plasma CoQ10 (Svete et al., 2017). Secondly, based on a previous study (Freeman et al., 2005), CoQ10 may protect cardiomyocytes from injury through its antioxidant action. Thirdly, CoQ10 was found to decrease vascular resistance via preventing nitric oxide destruction and therefore allowed blood flow from the heart to move forward more easily (van den Heuvel et al., 2000). The improved systolic function was not observed in group II dogs (B.W. ≥ 6 kg). Since the recommended dose of CoQ10 (Dove, 2001) was given per dog, not per body weight, we think that the dose given to group II dogs was not enough to see the effect. Therefore, we suggest that a supplementation of CoQ10 in dogs should be calculated from the body weight of the dog. The limitation here in this study is that we did not measure the serum concentration of CoQ10 in MMVD dogs. Our speculation needs further investigation.

Cardiac troponin I is a specific biomarker for cardiomyocyte injury (Liquoriet al., 2014). Upon sarcolemmal membrane rupture during injury, the free cardiac troponin I is released into the circulation. In canines, cTnI can be detected as early as 4 hours and peaks at 10 to 16 hours after experimentally induced myocardial infarction (Well and Sleeper, 2008). The half-life of cTnI is around 70 minutes (Jaffe et al., 1996). Therefore, the increased cTnI level at the beginning of the experiment in dogs may reflect an ongoing release of cTnI due to a continuous remodeling process, rather than an acute myocardial injury. Previous reports have shown that a high level of cTnI in serum has been found, in mitral valve diseases (Oyama and Sission, 2004; Falk et al., 2013). Similarly, we found that sixty

percent of the MMVD dogs in the current study had elevated cTnI concentrations. The cardioprotective effect of CoQ10 was tested after 28 days of receiving CoQ10 and showed that seventy percent of these dogs had a lower cTnI level. Despite this, there was no statistical difference between the before and after group but cTnI seemed to be lower in the CoQ10 supplementation group. However, this result is in agreement with a few previous reports in human (Taggart el al., 1996; Aslanabadi et al., 2016) in which cardiac biomarkers (i.e. myoglobin, creatine kinase, cTnT, and cTnI) did not significantly change in patients who had undergone heart operations with short-term CoQ10 supplementation. Therefore, it is likely that cardiac biomarkers may not be a sensitive method for detecting the cardioprotective effect of CoQ10 clinically.

HRV is a noninvasive tool for evaluating the activities of the ANS and also provides a powerful way to observe the relationship between the sympathetic and parasympathetic nervous system. Certain parts of the spectral components of HRV are known as a reflection of possibilities of ANS to modulate heart rate. The high frequency (HF) component of HRV representing parasympathetic activity and the low frequency (LF) component of HRV representing sympathetic or both mixed sympathetic and vagal modulation activities (Rajendra Acharya et al., 2006). LF/HF ratio is proposed as a measurement of sympathovagal activity balance (Malliani et al., 1991). A higher LF/HF ratio means a predominant sympathetic activity stage. On the other hand, a lower LF/HF ratio reflects the predominance of vagal modulation activity (Milicevic, 2005). At present, there are only a few studies that have investigated HRV in symptomatic dogs with MMVD (Oliveira et al., 2012; Rasmussen et al., 2014). Those studies indicated either a decrease in parasympathetic activity or increased sympathetic modulation of HR in MMVD dog with HF. In the current pilot study, we found that CoQ10 supplementation in MMVD dogs had no effect on HRV parameters and hence autonomic function was unaltered. This result may imply that either CoQ10 had no direct effect on autonomic function or it may prevent a vicious chronic sympathetic activation found in HF patients. However, in our study, LF/HF ratio was found to correlate positively with cTnI level. This result suggests that with low sympathetic activation, the cardiac muscle is likely to be less damaged. Moreover, LF/HF ratio had a tendency to correlate negatively with FS in dogs after CoQ10 prescription. This result also implies that CoQ10 improved systolic function independent of sympathetic activation (i.e. via enhancement of ATP production). The effect of CoQ10 on HRV was studied in healthy human subjects (Zheng and Moritani, 2008). The study discovered that during exercise, subjects with CoQ10 supplementation had an enhanced over-all ANS activity as indicated by total power. However, the mechanism by which CoQ10 augmented ANS in human was unclear.

Limitations: We tried to minimize factors that may influence the study, therefore, drugs previously reported to affect the HRV were excluded from our study (e.g. digitalis, beta-blocker, and spironolactone) (Shehab et al., 2008). However, dogs still received other medication (i.e. enalapril and/or furosemide) since these dogs were under cardiac therapy and represented routine cases in clinical practice. The effect of enalapril on HRV was reported previously (Chompoosan et al., 2014) in which in asymptomatic MMVD dogs (stage B1 or B2), enalapril decreased sympathetic tone after 14 days. On the other hand, we did not observe changes in sympathetic tone even though these dogs were also prescribed with enalapril. This can be explained by the following reasons. Our studied population were symptomatic MMVD dogs which had different backgrounds of sympathetic activity. The dogs in our study had already been given enalapril before the study. The direct effect of enalapril on HRV in stage C MMVD dogs had not been tested before. Moreover, studies in humans showed that ACE inhibitors did not alter vagal tone as assessed by HRV (Packer, 1985). The effect of furosemide on HRV has not been tested elsewhere. Whether this drug may influence tested parameters is unknown. Nevertheless, we believed that both enalapril and furosemide had a minimal effect on our results. However, the Holter analysis software was designed for use in humans which added some limitations to the Holter analysis.

In summary, the clinical benefit after 4 weeks-CoQ10 supplementations in MMVD dogs with the symptom of HF is the improvement of systolic function. CoQ10 did not alter sympathovagal balance in MMVD dogs. The cardio-protective effect of CoQ10 was not observed. Supplementation dose of CoQ10 should be based on the body weight. The large randomized clinical trials are needed to ensure this beneficial effect.

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บทคัดย่อ

ผลของการเสริมโคเอนไซม์คิว 10 ต่อระดับคาร์ดิแอคโทรโปนินไอ ความแปรปวนของอัตราการเต้นหัวใจและค่าของคลื่นเสียงสะท้อนหัวใจในสุนัขที่มีภาวะลิ้นหัวใจไมทรัลเสื่อมแบบมิกซ์โซมาตัส: การศึกษานำร่อง

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ประโยชน์ทางคลินิกของโคเอนไซม์คิว 10 (CoQ10) ได้ถูกรายงานอย่างเป็นอย่างดีในผู้ป่วยที่มีภาวะหัวใจล้มเหลว อย่างไรก็ตามในทางสัตวแพทย์นั้น ประโยชน์ทางคลินิกของ CoQ10 ในสุนัขที่เป็นโรคหัวใจยังไม่ปรากฏชัดเจนนัก การศึกษาครั้งนี้มีเป้าหมายเพื่อประเมินถึงผลของการเสริม CoQ10 ต่อ 1) การป้องกันการบาดเจ็บของกล้ามเนื้อหัวใจ 2) การทำงานของหัวใจ 3) สมดุลของระบบประสาทอัตโนวัติในสุนัขที่ทีภาวะลิ้นหัวใจไมทรัลเสื่อมแบบมิกซ์โซมาตัส (MMVD) สุนัข 13 ตัวที่มีภาวะ MMVD ในระยะ C ตามเกณฑ์ของ ACVIM ถูกใช้ในการศึกษาครั้งนี้ สุนัขได้ถูกแบ่งเป็นกลุ่มที่ 1 (น้ำหนักตัวน้อยกว่า6 กิโลกรัม จำนวน 7 ตัว) และกลุ่มที่ 2 (นน. ตัวน้อยมากกว่าหรือเท่ากับ 6 กิโลกรัม จำนวน 6 ตัว) ทำการวัดระดับคาร์ดิแอคโทรโปรตินไอ (cTnI), คลื่นเสียงสะท้อนหัวใจและการวัดคลื่นไฟฟ้าหัวใจต่อเนื่อง (Holter recording) เป็นเวลา 2 ชั่วโมง ในวันที่ 0 และหลังจากสุนัขได้รับ CoQ10 ในขนาด 100 มิลลิกรัมต่อตัวเป็นเวลาสองครั้งทุกวันเป็นระยะเวลา 28 วัน CoQ10 ทำให้ระดับ cTnI ลดลงร้อยละ 71 ในสุนัข ค่ามัธยฐานของ cTnI มีแนวโน้มที่ลดลงแต่ไม่มีนัยสำคัญ ความสามารถในการบีบตัวของกล้ามเนื้อหัวใจ (สัดส่วนการหดสั้น [FS] และสัดส่วนการบีบเอาเลือดออกไป [EF]) เพิ่มขึ้นอย่างมีนัยสำคัญ ร้อยละ 8 และ ร้อยละ 9 ตามลำดับ ในสุนัขกลุ่มที่ 1 หลังจากได้รับการเสริม CoQ10 ค่าพารามิเตอร์อื่นๆของคลื่นเสียงสะท้อนหัวใจไม่มีการเปลี่ยนแปลงในทั้งสองกลุ่ม การวิเคราะห์ความแปรปวนของอัตราการเต้นของหัวใจ (HRV) พบว่าไม่มีการเปลี่ยนแปลงของสมดุลย์ของระบบประสาทอัตโนวัติ ค่า cTnI มีความสัมพันธ์แบบเป็นลบกับค่า FS ($P < 0.01$) และสัมพันธ์แบบเชิงบวกกับค่าอัตราส่วน LF/HF ($P < 0.05$) โดยสรุปการศึกษาครั้งนี้แสดงให้เห็นถึงประโยชน์ทางคลินิกของการเสริม CoQ10 ในสุนัขทีมีภาวะ MMVD โดย CoQ10 ช่วยเพิ่มการทำงานของหัวใจในสุนัขขนาดเล็กที่มีภาวะ DMVD และท้ายที่สุดการเสริม CoQ10 ควรให้ตามขนาดของน้ำหนักตัวสุนัข

คำสำคัญ: คาร์ดิแอคโทรโปนินไอ โคคิวเอนไซม์คิว 10 สุนัข ความแปรปวนของอัตราการเต้นหัวใจ ลิ้นหัวใจเสื่อมแบบมิกซ์โซมาตัส

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