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<Original Article>

Serum serotonin concentration in lean and obese dogs with myxomatous mitral valve disease

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Abstract: The aim of the present study is to investigate the potential influence of obesity as a factor in 5-hydroxytryptamine (5-HT) concentration in myxomatous mitral valve disease (MMVD) dogs. Fifty-five client-owned dogs were enrolled in a randomized trial. Dogs were classified by echocardiography into healthy (control), mild, and moderate to severe MMVD groups. Each group was subclassified by using a 9-point body condition score (BCS); lean (BCS 5–6/9) and obese groups (BCS 7.5–9/9). Dogs with moderate to severe MMVD had lower serotonin (5-HT) concentrations than the control group ($p = 0.03$). Dogs with moderate to severe MMVD ($p = 0.017$) had lower serum 5-HT concentrations than the control group in the obese group (BCS 7.5–9/9). Significant difference was found between the lean and obese groups ($p = 0.015$) which are not consider severe in the MMVD group. These results suggested that 5-HT concentration was decreased with the increasing severity of MMVD, and obesity might be taken into consideration when interpreting the serotonin concentration in MMVD dogs.

Keywords: 5-HT concentration, body condition score, dogs, myxomatous mitral valve disease, obesity

Introduction

Serotonin (5-hydroxytryptamine or 5-HT) is known as a monoamine neurotransmitter biologically derived from tryptophan, and is mainly found in the gastrointestinal tract, platelet, and in the central nervous system of animals including humans [14]. Approximately 90% of 5-HT in the body is synthesized in the enterochromaffin cells of the intestine [10]. 5-HT is associated with numerous biological functions on mood, appetite, and the cardiovascular system [6]. In relation to appetite, 5-HT interacts with leptin, the first identified adipokine. In the cardiovascular system, it has been recently reported that 5-HT has a role in the development of mitral valve disease [11]. 5-HT-related mechanism which is increased 5-HT signaling or decreased 5-HT clearance may lead to valvulopathy in humans and animal models. It is associated with valvular lesions in humans with carcinoid tumors, or in those receiving serotonergic drugs [2,4]. Long term administration of 5-HT also develops valvular lesions in rats [3, 5]. Myxomatous mital valve disease (MMVD) is one of the most common heart disease in dogs [3]. It has been suggested that MMVD is functionally and pathologically similar in humans and dogs [13]. In a previous study, increased circulating 5-HT concentration as a potential source of heightened 5-HT signaling was demonstrated in small dogs with MMVD [11]. 5-HT concentration was decreasing with the increase of MMVD severity [13]. Another study demonstrated no significant difference in the 5-HT concentration of dogs with MMVD compared to healthy dogs [9]. Therefore, the aim of the present study is to investigate the potential influence of obesity to 5-HT concentration in MMVD dogs.

Materials and Methods

Study population

Three populations of client-owned dogs were prospectively recruited at the Veterinary Medical Teaching Hospitals of Chungnam National University, Konkuk University and Kangwon National University between May 2013 and July 2014. Fifty-five dogs (22 males and 33 females) were enrolled in the current study. The control group consisted of 15 dogs with 2 mixed breeds, 1 Bedlington terrier, 1 Borzoi, 1 Boxer, 4 Yorkshire terriers, and 6 Beagles. The MMVD groups consisted of 41 dogs with evidence of MMVD on echocardiography and 20 dogs that had mild MMVD and, 21 dogs that had severe MMVD. Each group classified by a body condi-

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Table 1. Signalments of control and myxomatous mitral valve disease (MMVD) groups (mean ± SE)

Items	Control group		Mild group		Moderate to severe group	
	Lean	Obese	Lean	Obese	Lean	Obese
Number of samples	7	7	12	8	14	7
Sex (male/female)	3/4	5/2	4/8	0/8	7/7	3/4
Age (yr)	7 ± 1.63	6.14 ± 1.6	10.75 ± 1.54	12.57 ± 1.59	10.42 ± 1.91	11 ± 1.29
Body weight (kg)	7.7 ± 6.1	10.7 ± 3.4	4.6 ± 2.95	7.37 ± 1.78	5.96 ± 6.94	7.14 ± 2.57

tion score (BCS) (Table 1) consisted of the control group (7 lean, 7 obese), the mild group (12 lean, 8 obese), and the moderate to severe group (14 lean, 7 obese). The most commonly recruited breeds in MMVD group were Maltese (n = 13) and Shih-Tzu (n = 13) followed by Yorkshire Terrier (n = 4), Cocker Spaniel (n = 3), Mixed (n = 3), Pekinese (n = 1), and Pomeranian (n = 1).

All owner's consents were obtained prior to evaluation and blood collection. As inclusion criteria for the present study, dogs were included if they had evidence of MMVD or an absence (control) of physical or echocardiographic evidence of MMVD. Dogs with congenital heart disease or significant systemic disease were excluded from this study. Also, dogs receiving serotonergic drugs, such as fluoxetine or being fed serotonin-containing foods (*i.e.*, bananas, tomatoes, pineapples, or walnuts) were not included in this study.

The raw data (an owner interview, physical examination, blood collection, and echocardiography) were collected from each dog. All examinations were performed without sedation in a quiet examination room. Each investigator weighed and determined BCS and assigned the dog to either the control (lean) group (BCS 4–5/9) or the obese group (BCS 7.5–9/9) utilizing a 9-point BCS system [7].

Five milliliters of blood was collected from the cephalic vein into a serum tube. Serum samples were separated by centrifugation and transferred into Eppendorf tubes. Serum samples were stored at −80°C for batched analysis.

Sample grouping and sandwich ELISA test

Echocardiography was performed to verify the diagnosis of MMVD and to assess the severity of MMVD. The left atrial to aortic root ratio was measured from the right 2-dimentional short-axis view. The M-mode values of the left ventricle were measured as previously described and obtained from the right parasternal short axis view [1]. Estimations of MMVD severity based on the obtained left atrium (LA)/aortic root (Ao) ratio and presence of mitral regurgitation (MR) were classified as follows: control group (LA : Ao ratio ≤ 1.5 with no MR), mild group (LA : Ao ratio ≤ 1.5 with MR), and moderate and severe group (LA : Ao ratio > 1.5 with MR).

Serum 5-HT concentrations were measured by a commercially available serotonin ELISA kit (Enzo Life Sciences, USA) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed by a commercially available computer-based software program (SPSS Statistics 18.0.0; SPSS, USA). Serum 5-HT concentrations are presented as the average values of each group within standard error (mean ± SE). A p value of < 0.05 was considered significant. The one-way ANOVA was used to investigate overall associations between 5-HT concentration and the control and 2 MMVD groups. If a significant association ($p < 0.05$) was detected, a pair-wise comparison was performed by use of the Duncan-test.

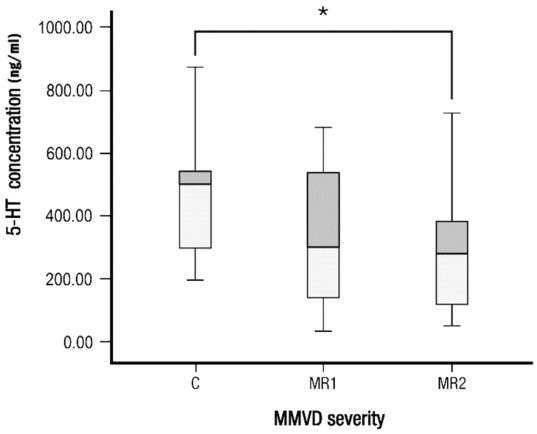

Fig. 1. Association of serum 5-HT concentration in control (C) and 2 MMVD groups (MR1, mild; MR2, moderate to severe). Error bars represent standard errors. *Significant difference was observed between two groups ($p < 0.05$).

Results

5-HT concentration were decreased with the increasing of severity of MMVD (Fig. 1). Lower 5-HT concentrations were significantly observed in dogs with moderate to severe MMVD ($p = 0.03$) compared with the control group (Fig. 1). However, there was no significant difference ($p = 0.102$) between control group and the mild group, and no significant difference ($p = 0.83$) was found in dogs with moderate to severe MMVD compared with mild MMVD group. Significant difference was observed between the lean and the obese groups ($p = 0.015$), which were not considered severity in the MMVD group (Fig. 2A). No difference ($p = 0.335$) was found between females and males (Fig. 2B). In the lean group (BCS 5–6), no significant differences were found among the control, mild and moderate to severe groups with MMVD (Fig. 2C). In the obese group (BCS 7.5–9), significantly lower 5-HT

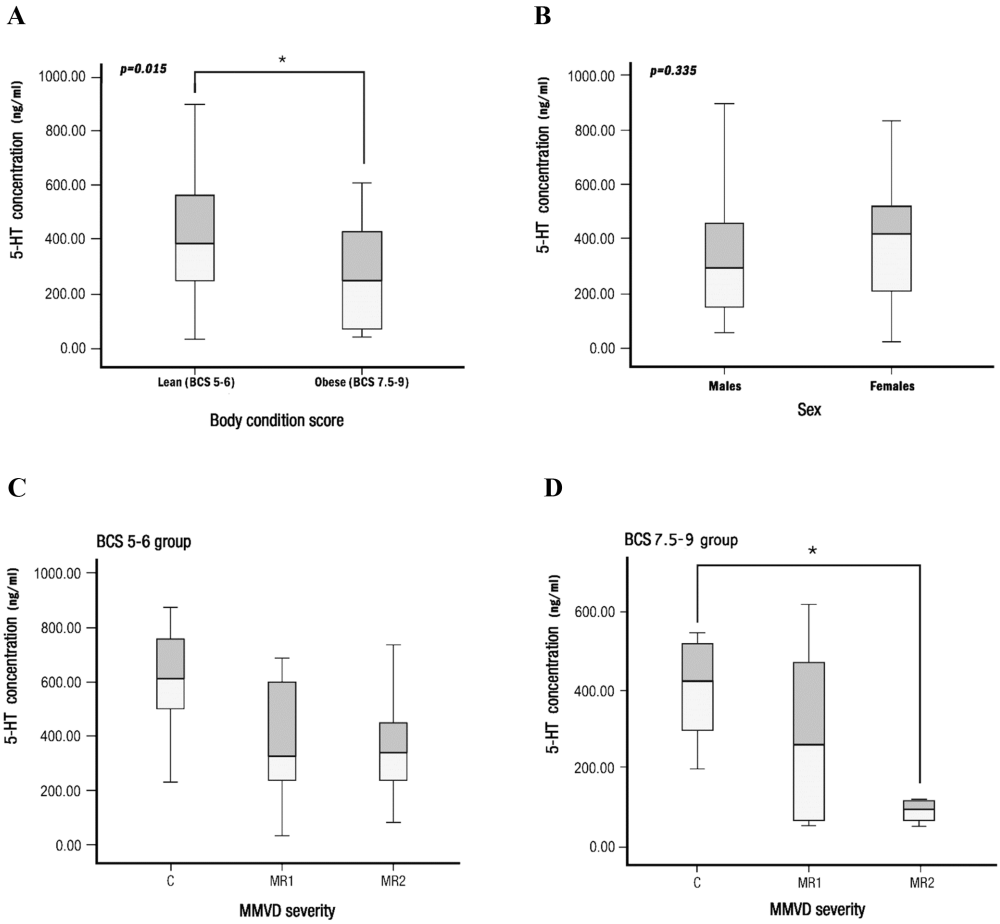

Fig 2. Association of lean and obese states (A), sex (B), lean BCS with MMVD severity (C), and obese BCS with MMVD severity (D). *Significant difference was observed between two groups ($p < 0.05$).

concentrations were observed between the control and the moderate to severe MMVD groups (Fig. 2D), although no significant difference was observed between the control group and the mild MMVD group.

Discussion

Recently, 5-HT has been suggested to have a role in the development of MMVD in dogs [8, 9]. The mitral valve leaflets are naturally thin, translucent, thickening and elongation with disease progression, which can lead to MMVD in dogs [13]. 5-HT concentration was decreasing with the increase of MMVD severity, from which might be suggested that if 5-HT plays a role in valvular degeneration it does so primarily in the early stages of the disease [13]. However, one study demonstrated no significant difference in the 5-HT concentration of dogs with MMVD compared to healthy dogs [9].

For these reasons, we had questions concerning other potential source effects on 5-HT concentration in MMVD dogs. In the present study, low 5-HT concentration was found with an increase of MMVD severity. A significant low 5-HT concentration was found between control and moderate to severe groups, although there were no differences between the control and mild group, and between the mild and the moderate to severe group. These findings are similar to the previous study that 5-HT concentration was decreasing with increasing MMVD severity and high 5-HT levels in early stages of MMVD are associated with the development of MMVD [8].

In the present study, low 5-HT concentration was significantly observed in obese groups compared to lean groups. The result is similar to previous study suggesting that low 5-HT concentration is associated with increasing risk of obesity [12]. Furthermore, the obese group with moderate to severe MMVD had lower 5-HT concentration than obesity dogs with no MMVD in the present study, although there was no difference with lean dogs in MMVD severity. There were a few limitations of the present study. Samples obtained from the obese dogs in moderate to severe MMVD group were of a small sample size. Further study should be performed using larger samples and in relation to the potential influence of obesity in the 5-HT concentration of MMVD dogs.

In conclusion, 5-HT concentration was decreased with the increasing in severity of MMVD. The result is similar to that

of Ljungvall [8]. Also, dogs with moderate to severe MMVD had significantly lower serum 5-HT concentrations than the control group in the obese groups. The results indicate that the obesity factor might be taken into consideration when interpreting test results of serotonin concentration in MMVD dogs.

Acknowledgments

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