Left ventricular geometric characteristics predict response to carvedilol in cats with asymptomatic hypertrophic obstructive cardiomyopathy caused by systolic anterior motion of the mitral valve

Yohei MOCHIZUKI[1,2]*, Ryohei SUZUKI[1], Yuyo YASUMURA[1], Takahiro SAITO[1], Takahiro TESHIMA[1], Hirotaka MATSUMOTO[1] and Hidekazu KOYAMA[1]

[1)]Division of Therapeutic Science 1, Department of Veterinary Clinical Medicine, Faculty of Veterinary Medicine, Nippon Veterinary and Life Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 184-8602, Japan
[2)]Faculty of Veterinary Medicine, Okayama University of Science, 1-3 Ikoinooka, Imabari-shi, Ehime 794-8555, Japan

ABSTRACT. Beta-blockers are used to treat cats with hypertrophic obstructive cardiomyopathy (HOCM). However, there are various hemodynamic responses to beta-blockers. This retrospective study aimed to explore the relationship between the response to carvedilol and the presence of geometric abnormalities. Medical records were reviewed for 16 cats diagnosed with HOCM. Cats were divided into two groups based on the velocity of the left-ventricular outflow-tract after carvedilol treatment (responder: eight cats, non-responder: eight cats). Baseline intergroup comparison revealed that anterior mitral valve leaflet length and diastolic left-ventricular posterior-wall thickness were significantly greater in the non-responder group. Longer anterior mitral valve leaflet and thicker left-ventricular posterior-wall may cause poor response to carvedilol. Thus, these properties may predict a lack of response to carvedilol therapy.

KEY WORDS: carvedilol, feline, geometry, hypertrophic obstructive cardiomyopathy, systolic anterior motion

Hypertrophic cardiomyopathy (HCM) is the most common myocardial disease in cats, and varies in both phenotype and clinical outcome [8]. Systolic anterior motion (SAM) of the mitral valve leaflet causes dynamic left-ventricular outflow-tract obstruction (DLVOTO) [9]. In humans, SAM is reportedly related to severe left-ventricular and papillary muscle hypertrophy [10]; papillary muscle anterior displacement [14]; increased distance between anterior and posterior papillary muscles [10]; elongation of the mitral valve anterior leaflet, posterior leaflet, or both [13]; abnormal chordae tendineae attachment [21]; reduced distance between the interventricular septum and coaptation point of the mitral valve [19]; and a reduced angle between the interventricular septum and the aorta [13]. A recent study found that the above abnormalities in left-ventricular geometry are associated with the presence of DLVOTO in cats with HCM [17]. Although beta-blockers have not been reported to provide beneficial outcomes for cats with HCM, they have been used in veterinary medicine to reduce heart rate, arrhythmia frequency, and outflow-tract gradients [12, 18]. A recent report indicated that atenolol failed to show an effect in cats with HCM [18]. Carvedilol has been reported as effective treatment for human patients with chronic heart failure [16]. Additionally, previous reports have shown that carvedilol reduces the incidence of myocardial infarction and protects against lethal reperfusion injury in feline models [2–4]. Therefore, carvedilol may be an effective therapeutic agent for cats with HCM. However, administration of beta-blockers to humans does not consistently reduce the blood flow velocity of the left-ventricular outflow-tract [7, 22]; similarly, inconsistent treatment efficacy has been reported in cats [5]. We hypothesized that the beta-blocker response is dependent upon DLVOTO severity associated with geometric abnormalities, including base-level interventricular septal wall thickening, prolonged mitral valve leaflet, and papillary muscle hypertrophy. This study aimed to explore whether geometric characteristics in DLVOTO impact the carvedilol response in cats with hypertrophic obstructive cardiomyopathy (HOCM). To the best of our knowledge, this hypothesis has not yet been tested, and its validation would help to guide therapeutic planning for cats with DLVOTO.

In the present study, we reviewed the medical records of 28 cats that were diagnosed with asymptomatic HOCM and treated

*Correspondence to: Mochizuki, Y.: y-mochizuki@vet.ous.ac.jp
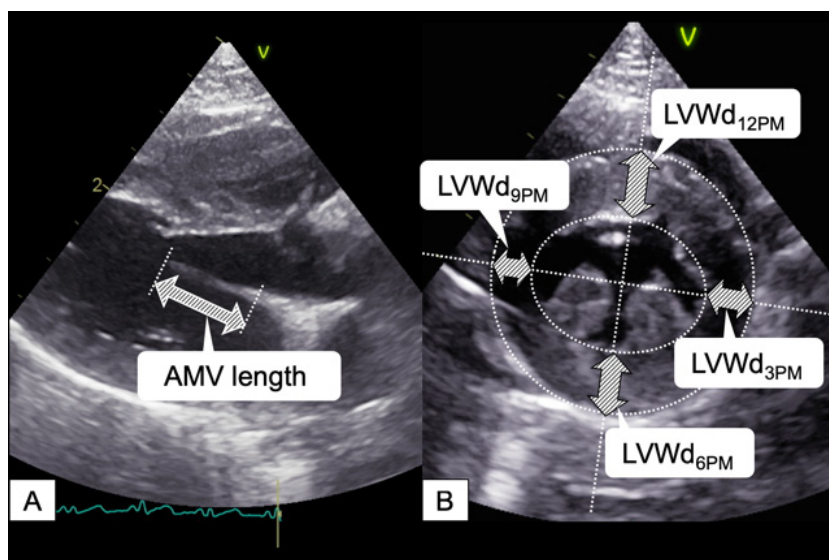
Fig. 1. Measurement example of echocardiographic variables. (A) Anterior mitral valve length (AMV length) was measured at mid-diastole. (B) End-diastolic left-ventricular wall thickness was divided into four segments at 3PM, 6PM, 9PM, and 12PM, and was measured from papillary muscle level short axis view (LVWd$_{3PM}$, LVWd$_{6PM}$, LVWd$_{9PM}$, and LVWd$_{12PM}$, respectively).

with carvedilol (Artist, Daiichi Sankyo Co., Ltd., Tokyo, Japan), during the period from October 2010 to February 2016, at the Veterinary Medical Teaching Hospital of the Nippon Veterinary and Life Science University. Diagnostic criteria for HOCM were defined as previously reported: interventricular septal and/or left-ventricular posterior-wall thickness at end diastole >6 mm, as observed via the left-ventricular short-axis view at the level of the chordae tendineae; peak velocity of left-ventricular outflow-tract (LVOT Vmax) >2.5 m/sec; SAM of mitral valve leaflet on B-mode; and absence of other complications, including other cardiac disease, dehydration, and/or systemic disease influencing circulation [12, 23]. Physical examination, electrocardiography, thoracic radiography, blood pressure measurement, and echocardiography were performed before (baseline) and after carvedilol treatment. Carvedilol doses were gradually increased until the maximum tolerable dose was reached, or until systolic murmur disappeared. Carvedilol doses were less than or equal to those in a previous report [24]. Re-examination data after carvedilol administration were acquired at least 1 week after the maximum carvedilol dose had been reached for each cat. All cats were divided into two groups based on LVOT Vmax in the post-administration examination: responder group (LVOT Vmax decreased to <2.5 m/sec) and non-responder group (LVOT Vmax remained >2.5 m/sec).

Echocardiography was performed by two cardiologists with an ultrasound machine (Vivid 7 and Vivid E95, GE Healthcare Japan, Tokyo, Japan) that was equipped with a 7-MHz or 12-MHz phased array probe. All cats were held gently in the lateral position during examinations. At least five cardiac cycles of B-mode data were acquired. All echocardiographic variables were measured by one observer, who was not a member of the cardiology team that performed echocardiography, using off-line workstation software (EchoPAC PC v2.0.1, GE Healthcare Japan). The average value of three continuous cardiac cycles was used for statistical analysis.

In accordance with the methods of previous reports, left-ventricular geometrical parameters were measured on parasternal left-ventricular long-axis view. These parameters were as follows: base- and mid-level interventricular septum thickness (base-IVSd and mid-IVSd), left-ventricular posterior-wall thickness at end-diastole (LVPWd), and left-ventricular internal dimension at end-diastole and end-systole (LVIDd and LVIDs) [17]. Anterior mitral valve leaflet length (AMV length) was measured at mid-diastole (Fig. 1A) [17]. The angle between the interventricular septum and ascending aorta (Angle IVS-Ao) was measured [17]. The dimensions of the four segmental walls were measured from the left-ventricular short-axis view at end-diastole (LVWd$_{3PM}$, LVWd$_{6PM}$, LVWd$_{9PM}$, and LVWd$_{12PM}$, respectively; Fig. 1B) [17]. At the left-ventricular short-axis view of papillary muscle level, the anterior, posterior, and accessory papillary muscle area (PPM area) was measured by direct tracing on images [1]. In a repeatability study, which was conducted by triplicate measurements at 1-week intervals in 10 cats, the coefficient variables of echocardiographic parameters were less than 10%. Blood pressure was measured using the oscillometric method (BP100D, Fukuda M-E Kogyo Co., Ltd., Tokyo, Japan). Heart rate was determined by using electrocardiographic data acquired on the same day.

All categorical variables were described as total numbers, and continuous variables were described as median and interquartile ranges. For analysis of categorical data, Fisher's exact test was used. To compare the responder and non-responder groups, the Mann-Whitney U test was used. To assess intragroup changes between baseline and post-treatment assessments, the Wilcoxon signed-rank test was used. To correct type I error, P values were adjusted using the Bonferroni method. All P values <0.05 were considered to be statistically significant. All statistical analysis was performed using a commercial software package (IBM SPSS statistics ver. 25, IBM Japan, Tokyo, Japan).

Of the 28 cats considered, three were excluded from this study because they were treated with other medications that affected

Table 1. Characteristics of cats in each group at the baseline examination, shown with carvedilol dose and dosing period

	Responder group	Non-responder group
Number of cats	8	8
Age (year)	1.3 [0.8–1.6]	2.5 [1.5–3.5][a]
Male / female	4/4	6/2
Body weight (kg)	3.6 [3.4–4.1]	4.0 [3.5–4.6]
Carvedilol dose (mg/kg/day)	0.20 [0.2–0.5]	0.36 [0.2–0.5][a]
Dosing period (days)	106.5 [86.8–257.0]	106.5 [31.0–203.0]

All categorical data are shown as totals, and continuous variables were shown as median and interquartile ranges. The non-responder group featured a significantly higher age and carvedilol dose, relative to the responder group. a) Responder vs. Non-responder, $P<0.05$.

Table 2. Heart rate, blood pressure, and echocardiographic variables before and after carvedilol treatment

	Responder group		Non-responder group	
	Baseline	After treatment	Baseline	After treatment
Heart rate (bpm)	217 [190–223]	171 [153–179][b]	194 [179–209]	165 [146–181][b]
Blood pressure (mmHg)				
Systolic BP	124.0 [110.5–146.0]	149.0 [145.0–161.0]	125.0 [115.1–134.3]	143.0 [122.0–150.0]
Mean BP	89.5 [77.8–113.3]	111.0 [98.0–119.0]	94.5 [90.5–101.5]	110.0 [82.0–115.0]
Diastolic BP	72.0 [63.0–95.5]	91.0 [80.0–102.0]	76.0 [71.3–88.3]	82.0 [64.0–96.0]
Echocardiographic variables				
LVOT Vmax (m/sec)	3.7 [3.6–4.0]	1.0 [0.9–1.3]	4.5 [4.3–5.1][a]	4.5 [3.8–5.2]
LA:Ao	1.3 [1.2–1.4]	1.2 [1.1–1.2]	1.4 [1.3–1.5]	1.6 [1.4–1.7]
Base-IVSd (mm)	7.1 [5.8–8.1]	6.4 [6.2–7.2]	8.0 [7.6–9.0]	9.1 [8.1–9.8]
Mid-IVSd (mm)	6.5 [5.6–7.5]	5.7 [5.1–6.1]	7.9 [7.6–8.7]	7.6 [7.1–8.0]
LVIDd (mm)	11.8 [11.0–13.0]	14.1 [13.1–14.8][b]	11.7 [10.1–12.8]	12.9 [10.4–13.9][b]
LVIDs (mm)	6.1 [5.9–8.3]	7.0 [5.9–7.8]	6.2 [4.7–7.1]	8.3 [6.9–9.0][b]
LVPWd (mm)	5.3 [5.0–6.1]	4.3 [4.1–5.3][b]	7.4 [7.2–7.4][a]	6.8 [6.3–7.4]
$LVWd_{3PM}$ (mm)	4.7 [4.3–4.9]	4.5 [4.2–4.6]	6.0 [4.4–6.3]	5.4 [5.0–5.6]
$LVWd_{6PM}$ (mm)	4.6 [3.7–5.2]	4.3 [3.8–4.7]	6.4 [6.1–7.9][a]	6.3 [5.7–7.5]
$LVWd_{9PM}$ (mm)	4.8 [4.6–5.2]	4.0 [3.9–4.9]	5.9 [5.3–6.3][a]	5.5 [4.7–6.1]
$LVWd_{12PM}$ (mm)	6.0 [5.8–6.3]	5.5 [5.3–5.9]	6.8 [6.1–7.3]	6.7 [5.9–7.1]
AMV length (mm)	10.1 [9.6–10.9]	10.0 [9.5–10.4]	12.6 [11.8–13.6][a]	12.3 [11.7–12.8]
Angle IVS-Ao (°)	135.5 [130.0–139.3]	125.9 [125.0–129.3]	135.4 [131.4–139.9]	131.7 [129.3–135.6]
PPM area (mm^2)	70.5 [56.9–84.7]	65.7 [57.0–75.5]	76.6 [62.4–90.0]	87.6 [72.4–99.3]

In both groups, heart rate was significantly decreased after carvedilol treatment. Blood pressure in both groups were not significantly changed. LVOT Vmax, maximum velocity of left ventricular outflow tract; LA:Ao, ratio of the left atrial dimension to the aortic annulus dimension; IVSd, interventricular septum thickness at end-diastole; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; LVPWd, left ventricular posterior wall thickness at end-diastole; AMV, anterior mitral valve leaflet; PPM, papillary muscle area; Systolic BP, systolic blood pressure; Mean BP, mean blood pressure; Diastolic BP, diastolic blood pressure. a) Responder group vs. Non-responder group, $P<0.05$. b) Baseline vs. After treatment, $P<0.05$.

hemodynamics (i.e., atenolol or diltiazem) before the baseline examination; nine other cats were excluded because they did not complete follow-up examinations. Thus, 16 cats with asymptomatic HOCM were included in this study. Based on the echocardiographic data acquired after carvedilol administration, all cats were classified into responder (n=8) and non-responder groups (n=8).

Profiles and comparisons of both groups at baseline, along with carvedilol dose and dosing period, are summarized in Table 1. Age and total dose of carvedilol were significantly higher in the non-responder group than in the responder group ($P<0.05$ for both).

Heart rate, echocardiographic variables, and blood pressure measured before and after carvedilol administration are summarized in Table 2. At baseline examination, the non-responder group demonstrated significantly higher LVOT Vmax, LVPWd, $LVWd_{6PM}$, $LVWd_{9PM}$, and AMV length, compared to the responder group ($P<0.05$, for all).

Carvedilol administration significantly decreased the LVOT Vmax of responder cats, whereas the LVOT Vmax remained unchanged in the non-responder group ($P<0.05$). Administration of beta-blocker significantly reduced heart rates and significantly increased LVIDd in both groups (responder group: $P<0.05$ for both; non-responder group: $P<0.05$ for both). LVPWd was significantly reduced in the responder group ($P<0.05$).

AMV length was significantly longer in the non-responder group than in the responder group. Whether this finding was caused by a primary geometric abnormality or by secondary elongation (e.g., due to DLVOTO mechanical stress) remains unclear. A human study reported that mitral-valve-anterior-leaflet deformation causes secondary elongation of mitral-valve length [15].
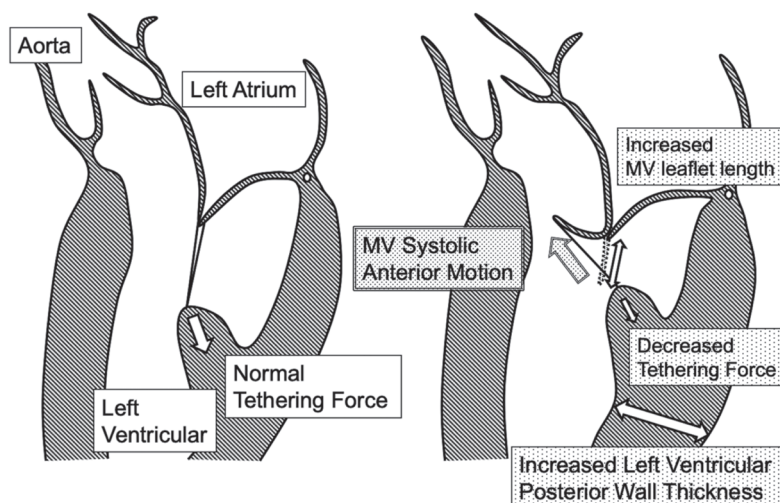
Fig. 2. Geometric specificity in the non-responder group is related to severe mitral valve systolic anterior motion. Schematic of the mechanism by which geometric abnormalities may cause more severe systolic anterior motion of the anterior mitral valve leaflet. Left-ventricular posterior-wall thickening could induce anterior displacement of the papillary muscle and reduce the tethering force of the mitral valve leaflet. Increased anterior mitral valve leaflet length would reduce the relative distance between the mitral valve leaflet and papillary muscle. Increased mitral valve leaflet immobility would thus cause severe systolic anterior motion.

Although mechanical stress may cause an elongated mitral leaflet, the lack of significant alteration of AMV length within the intragroup comparison suggests that the aforementioned deformation is a more likely cause. However, this relationship was unclear in the present study because of the small number of cats included in the analysis.

Recent experiments have demonstrated that SAM is not caused by the Venturi effect; in contrast, it is caused by abnormalities of papillary muscle geometry (i.e., hypertrophy and anterior displacement) [21]. The present study found no significant differences between the two groups in PPM area, which served as an indicator of papillary muscle hypertrophy. Although abnormal papillary muscle position was not assessed in this study, a divergent response to carvedilol treatment would not be caused by severe papillary muscle hypertrophy. Papillary muscle anterior displacement reportedly causes SAM in human patients without left-ventricular hypertrophy [11]. Papillary muscle hypertrophy may, therefore, be unrelated to displacement of the papillary muscle.

Schober *et al.* reported that the severity of DLVOTO is related to mitral valve leaflet length and left-ventricular wall thickness [21]. In non-responder cats, AMV length was significantly longer, and the parameters of left-ventricular posterior-wall thickness were significantly larger, compared to those same parameters for responder cats. Left-ventricular posterior-wall thickening may reduce the relative distance between the chorda tendinae attachment position of the papillary muscle and the mitral valve leaflet, due to anterior displacement of the papillary muscle. Additionally, elongation of the mitral valve leaflet would reduce tension on the chordae tendineae. Because of the reduction in relative distance between the papillary muscle and mitral valve leaflet, the tethering force on the mitral valve would be subsequently reduced and the mitral valve anterior leaflet immobility would be lost, resulting in the inversion of the leaflet and consequent SAM (Fig. 2). Therefore, SAM would be more severe in the non-responder group. Due to the severity of SAM, the tethering force necessary for maintenance of the normal arrangement of the mitral valve might be absent, irrespective of an increase in LVIDd by carvedilol. Therefore, cats that exhibit HOCM due to severe SAM are less likely to respond to carvedilol treatment. To improve hemodynamics, other treatments, such as myotomy, may be required [20].

The present study demonstrated a significant reduction in heart rate and a significant enhancement in LVIDd in both groups after administration of carvedilol, a non-selective beta-adrenergic receptor blocker. These alterations indicate that carvedilol induces a negative chronotropic effect and that the end-diastolic left-ventricular volume is increased due to a prolonged diastolic phase. Therefore, hemodynamic improvement in the responder group may not have been based on carvedilol susceptibility or bioavailability.

Cats in the non-responder group were significantly older than those in the responder group. Considering that the LVPWd, LVWd$_{6PM}$, and LVWd$_{9PM}$ were significantly thicker in the non-responder group than in the responder group, this may suggest that HCM had further progressed in the non-responder group. However, because the timing of the onset of HCM was unclear, we could not determine whether the non-responder group had experienced HCM for an extended duration.

This study had several limitations. Most importantly, it was retrospective; thus, we could not adjust the carvedilol dosing period or total dose. However, there was no significant variance in the dosing period; thus, it is unlikely that such differences affected our results. Additionally, the sample size was small, which diminished the power of the study for detection of differences between groups. It has also been reported that dehydration status influences ventricular-wall thickness and internal dimension [6]; this aspect may have impacted the results of the present study. However, all cats included in the present study had been diagnosed with asymptomatic HOCM and had no clinical signs of anorexia. Furthermore, cats with dehydration were excluded on the basis of physiological examination. We therefore minimized the effect of hydration in our study.

The diagnosis of HOCM in all cats included in this study was made by echocardiography; definitive diagnosis by pathological

examination was not performed. Notably, in our geometric assessment, all variables were based on echocardiography. This limitation indicates that our findings are not exhaustive; abnormalities undetectable by our methods may have affected the cats' responses to carvedilol treatment. Future research should adopt a design that permits investigation of other abnormalities that may influence response to carvedilol, particularly papillary muscle displacement.

In this study, all cats had asymptomatic HOCM; thus, we did not assess the effect of carvedilol treatment on clinical signs. Although left-atrial size was reduced in the responder group, we cannot definitively state whether carvedilol consistently affected the clinical symptoms of cats with HOCM in this study. Furthermore, outcome tracing was not performed; thus, the longitudinal effect of carvedilol therapy in cats remains unknown. Tracing longitudinal outcomes may clarify the value of carvedilol response as a prognostic factor in cats with HOCM.

The findings from this study suggest that cats experiencing HOCM with severe left-ventricular posterior-wall hypertrophy and prolonged AMV length may have severe SAM and be less likely to respond to carvedilol treatment.

REFERENCES

1. Adin, D. B. and Diley-Poston, L. 2007. Papillary muscle measurements in cats with normal echocardiograms and cats with concentric left ventricular hypertrophy. *J. Vet. Intern. Med.* **21**: 737–741. [Medline] [CrossRef]
2. Brunvand, H. and Grong, K. 1997. Carvedilol retards sudden loss of contraction during early regional myocardial ischemia in feline hearts. *J. Pharmacol. Exp. Ther.* **282**: 363–368. [Medline]
3. Brunvand, H., Kvitting, P. M., Rynning, S. E., Berge, R. K. and Grong, K. 1996. Carvedilol protects against lethal reperfusion injury through antiadrenergic mechanisms. *J. Cardiovasc. Pharmacol.* **28**: 409–417. [Medline] [CrossRef]
4. Brunvand, H., Frłyland, L., Hexeberg, E., Rynning, S. E., Berge, R. K. and Grong, K. 1996. Carvedilol improves function and reduces infarct size in the feline myocardium by protecting against lethal reperfusion injury. *Eur. J. Pharmacol.* **314**: 99–107. [Medline] [CrossRef]
5. Blass, K. A., Schober, K. E., Li, X., Scansen, B. A. and Bonagura, J. D. 2014. Acute effects of ivabradine on dynamic obstruction of the left ventricular outflow tract in cats with preclinical hypertrophic cardiomyopathy. *J. Vet. Intern. Med.* **28**: 838–846. [Medline] [CrossRef]
6. Campbell, F. E. and Kittleson, M. D. 2007. The effect of hydration status on the echocardiographic measurements of normal cats. *J. Vet. Intern. Med.* **21**: 1008–1015. [Medline] [CrossRef]
7. Cohen, L. S. and Braunwald, E. 1967. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* **35**: 847–851. [Medline] [CrossRef]
8. Fox, P. R. 2003. Hypertrophic cardiomyopathy. Clinical and pathologic correlates. *J. Vet. Cardiol.* **5**: 39–45. [Medline] [CrossRef]
9. Fox, P. R., Liu, S. K. and Maron, B. J. 1995. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy. An animal model of human disease. *Circulation* **92**: 2645–2651. [Medline] [CrossRef]
10. Harrigan, C. J., Appelbaum, E., Maron, B. J., Buros, J. L., Gibson, C. M., Lesser, J. R., Udelson, J. E., Manning, W. J. and Maron, M. S. 2008. Significance of papillary muscle abnormalities identified by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *Am. J. Cardiol.* **101**: 668–673. [Medline] [CrossRef]
11. Izgi, C., Akgun, T., Men, E. E. and Feray, H. 2010. Systolic anterior motion of the mitral valve in the absence left ventricular hypertrophy: role of mitral leaflet elongation and papillary muscle displacement. *Echocardiography* **27**: E36–E38. [Medline] [CrossRef]
12. Jackson, B. L., Adin, D. B. and Lehmkuhl, L. B. 2015. Effect of atenolol on heart rate, arrhythmias, blood pressure, and dynamic left ventricular outflow tract obstruction in cats with subclinical hypertrophic cardiomyopathy. *J. Vet. Cardiol.* **17** Suppl 1: S296–S305. [Medline] [CrossRef]
13. Kaple, R. K., Murphy, R. T., DiPaola, L. M., Houghtaling, P. L., Lever, H. M., Lytle, B. W., Blackstone, E. H. and Smedira, N. G. 2008. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. *Ann. Thorac. Surg.* **85**: 1527–1535, 1535.e1–1535.e2. [Medline] [CrossRef]
14. Krasnow, N. 1997. Subaortic septal bulge simulates hypertrophic cardiomyopathy by angulation of the septum with age, independent of focal hypertrophy. An echocardiographic study. *J. Am. Soc. Echocardiogr.* **10**: 545–555. [Medline] [CrossRef]
15. Ohkado, A., Kitamura, M., Hachida, M., Nishinaka, T., Hanayama, N., Sato, W. and Koyanagi, H. 1997. Hypertrophic obstructive cardiomyopathy with abnormalities of the mitral valve complex. *J. Heart Valve Dis.* **6**: 60–62. [Medline]
16. Poole-Wilson, P. A., Swedberg, K., Cleland, J. G., Di Lenarda, A., Hanrath, P., Komajda, M., Lubsen, J., Lutiger, B., Metra, M., Remme, W. J., Torp-Pedersen, C., Scherhag, A., Skene A., Carvedilol Or Metoprolol European Trial Investigators. 2003. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* **362**: 7–13. [Medline] [CrossRef]
17. Schober, K. and Todd, A. 2010. Echocardiographic assessment of left ventricular geometry and the mitral valve apparatus in cats with hypertrophic cardiomyopathy. *J. Vet. Cardiol.* **12**: 1–16. [Medline] [CrossRef]
18. Schober, K. E., Zientek, J., Li, X., Fuentes, V. L. and Bonagura, J. D. 2013. Effect of treatment with atenolol on 5-year survival in cats with preclinical (asymptomatic) hypertrophic cardiomyopathy. *J. Vet. Cardiol.* **15**: 93–104. [Medline] [CrossRef]
19. Shah, P. M., Taylor, R. D. and Wong, M. 1981. Abnormal mitral valve coaptation in hypertrophic obstructive cardiomyopathy: proposed role in systolic anterior motion of mitral valve. *Am. J. Cardiol.* **48**: 258–262. [Medline] [CrossRef]
20. Sherrid, M. V., Chaudhry, F. A. and Swistel, D. G. 2003. Obstructive hypertrophic cardiomyopathy: echocardiography, pathophysiology, and the continuing evolution of surgery for obstruction. *Ann. Thorac. Surg.* **75**: 620–632. [Medline] [CrossRef]
21. Sherrid, M. V., Balaram, S., Kim, B., Axel, L. and Swistel, D. G. 2016. The mitral valve in obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **67**: 1846–1858. [Medline] [CrossRef]
22. Sherrid, M. V., Shetty, A., Winson, G., Kim, B., Musat, D., Alviar, C. L., Homel, P., Balaram, S. K. and Swistel, D. G. 2013. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. *Circ Heart Fail* **6**: 694–702. [Medline] [CrossRef]
23. Suzuki, R., Mochizuki, Y., Yoshimatsu, H., Ohkusa, T., Teshima, T., Matsumoto, H. and Koyama, H. 2016. Myocardial torsional deformations in cats with hypertrophic cardiomyopathy using two-dimensional speckle-tracking echocardiography. *J. Vet. Cardiol.* **18**: 350–357. [Medline] [CrossRef]
24. Ukai, Y., Yamano, S., Toyofuku, T., Kodama, T. and Uechi, M. 2018. Cardiovascular effects of carvedilol in conscious healthy cats. *J. Vet. Cardiovasc. Med.* **1**: 1–5.