German Journal of Veterinary Research

eISSN:2703-1322

Research article

Assessment of soluble ST2 as a novel cardiac biomarker in cats with cardiomyopathy

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Article History:
Received: 22-Jun-2022
Accepted: 22-Aug-2022
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Abstract

Soluble suppression of tumorigenesis-2 (sST2), a member of the interleukin-1 receptor family, is a novel biomarker of mechanical stress that is measurable in serum. It has been shown in humans and animals to be physiologically related to cardiac hypertrophy, fibrosis, and ventricular dysfunction. This study aimed to evaluate sST2 levels in cats with cardiomyopathy. In addition, serum sST2 and other cardiac biomarker levels were compared. Twenty-four client-owned cats with hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy (RCM) were investigated. The cats included in the study were divided into four groups (I, II, III, and IV) according to the American College of Veterinary Internal Medicine (ACVIM) classification. Class B1 cats were included in group I (n=7), class B2 cats were included in group II (n=6), class C cats were included in group III (n=6), and healthy control-group cats in group IV (n=5). Measurement of cardiac troponin I (cTnI), cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sST2 levels, and echocardiographic examinations were performed in all groups, and correlations were investigated. We observed positive correlations among sST2 levels and CK-MB and LA diameter (p=0.05). There was no correlation between sST2, NT-proBNP, Troponin I, Troponin T, AST, and LDH levels. We confirmed positive correlations between NT-proBNP levels and LA diameter (p<0.05), CK-MB, IVSd, LVFWd, and LA/Ao ratio (p<0.01). Cardiac biomarkers have diagnostic significance for feline cardiomyopathies. There was no statistically significant difference in sST2 levels between the groups. However, further research is needed to investigate the relationship between the severity of cardiomyopathies and sST2 levels in cats.

Keywords: Cardiomyopathy, Biomarkers, NT-proBNP, Cat, sST2

Citation: Kaya, Y. and Bakırel, U. 2022. Assessment of soluble ST2 as a novel cardiac biomarker in cats with cardiomyopathy. Ger. J. Vet. Res. 2 (4): 1-7. https://doi.org/10.51585/gjvr.2022.4.0044

Introduction

Cardiomyopathies (CMs) are a heterogeneous group of myocardial diseases that can primarily or secondarily affect the heart and changeable phenotype and prognosis (Ferasin, 2009; Spalla et al., 2016; Luis Fuentes et al., 2020). CMs are common in cats, and cardiovascular disease is among the ten most common causes of death in cats (Fox et al., 2019; Luis Fuentes et al., 2020). According to The American College of Veterinary Internal Medicine (ACVIM) classification, the CMs in cats are classified based on structural and functional characteristics or phenotype.

Phenotypic classification of CMs is hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), unclassified cardiomyopathy (UCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Elliott et al., 2008; Luis Fuentes et al., 2020). Hypertrophic cardiomyopathy is common in cats and is a significant cause of congestive heart failure and cardiovascular diseases (Maron and Fox, 2015). Echocardiography is the gold standard in the diagnosis of cardiomyopathies and Doppler echocardiography can add additional information (Schober et al., 2003; Wood and Picard, 2004). However, echocardiography is time-consuming and technically demanding, and very few veterinarians specialize in echocardiography. Therefore, cardiac biomarkers are recommended when echocardiography is not available (Singletary et al., 2012).

Cardiac biomarkers application includes screening for preclinical cardiomyopathy, assessing the severity of the disease, and differentiating between cardiogenic and non-cardiogenic causes in cats with dyspnea. Currently, N-terminal pro-brain natriuretic peptide (NT-

proBNP), cardiac Troponin I (cTnI), and cardiac Troponin T (cTnT) are used as cardiac biomarkers of CMs in cats (Bakirel et al., 2021).

The search for a novel cardiac biomarker continues due to the limitations of available biomarkers. Troponins and natriuretic peptides may increase in non-cardiac diseases secondarily affecting the heart. Previous studies demonstrated that troponins and NT-proBNP concentration increase in cats suffering from hyperthyroidism, anemia, and renal disease (Menaut et al., 2012; Lalor et al., 2014; Sangster et al., 2014). Soluble suppression of tumorigenicity 2 (sST2) is a novel biomarker and can be found on cardiac myocytes and fibroblasts. ST2 is part of the interleukin (IL)-1 receptor family and the interaction between IL-33 and ST2 is protective and reduces fibrosis, hypertrophy, and apoptosis (Sanada et al., 2007; Biaggi et al., 2019).

Although sST2 appears to mediate myocardial fibrosis, an important pathogenetic process in cardiomyopathies, data about its usefulness in patients with CMs are limited. To our knowledge, no study has correlated the severity of CMs with sST2 levels in cats. Our primary goal was to determine the levels and diagnostic significance of sST2 levels in cats with cardiomyopathy. The secondary aim is to determine whether sST2 levels were correlated with NT-proBNP, cTnT, or cTnI and if they correlated with echocardiographic measures of left atrial (LA) and left ventricular (LV) size; with Doppler echocardiographic estimates of left ventricular filling pressure; and whether blood concentrations differed between various forms of cardiomyopathy.

Material and methods

Study population

Twenty-four cats that were admitted to the Istanbul University-Cerrahpasa, Faculty of Veterinary Medicine, Research and Teaching Hospital were used in the study. Radiography and echocardiographic evaluation were performed in cats with cardiomyopathy and the healthy-control group. Echocardiography was performed in all groups using a micro convex probe running at 7-9.3 mHz. The present study protocol was approved by the Istanbul University-Cerrahpasa Faculty of Veterinary Ethical Committee. The cat owner‘s consent to participate was obtained for all cats. Study cases were selected from cats that presented with acute dyspnea, presence of a cardiac murmur, arrhythmia, gallop sound, tachycardia, and tachypnoea (respiratory rate >40 breaths/min in cats), abnormal lung auscultation findings, and arterial thromboembolism (ATE). None of these cats were known to have medical conditions that would affect cardiac biomarker (sST2, Nt-proBNP, cTnT, cTnI AST, LDH, and CK-MB) concentrations. All cats were evaluated by echocardiography from standard views according to accepted techniques (Thomas et al., 1993; Fox et al., 2009).

The inclusion criteria were diagnosis of HCM, HOCM, and RCM on 2-dimensional (2D) echocardiography. A blood sample was taken after the examination. Cats included in the study were grouped as B1 (Group I), B2 (Group II), and C (Group III) according to the ACVIM classification. In this study, we evaluated separately Nt-proBNP, cTnT, cTnI AST, LDH, CK-MB, and sST2 levels in patients divided into four groups. Cats with concurrent systemic diseases such as renal failure, neoplasia, hyperthyroidism, or systemic hypertension were excluded. Cats receiving any medications (cardiac or non-cardiac) other than routine preventatives were excluded.

Clinical data

All cases included in this study were selected from cats with CMs. The age, sex, breed, and weight of all patients included in the study were recorded. The cats were divided into four groups according to the ACVIM classification. There are cats with the group I B1 (n=7) low-risk subclinical cardiomyopathy, group II (n=6) B2 high-risk cats, and group III (n=6) class C cats at risk of developing CHF or arterial thromboembolism (ATE). Group IV (n=5) is a healthy control group.

M-mode measurements of interventricular septal thickness at end-diastole (IVSd), left ventricular internal diameter in diastole and systole (LVIDd, LVIDs), and left ventricular free wall in diastole (LWFWd), left ventricular ejection fraction (LV %EF) and left ventricular shortening fraction (LV %FS) were at the level of the chordate tendineae in the short axis view. Left ventricular hypertrophy was defined when IVSd, LVPWd, or both equal or exceeded 6 mm (Ferasin, 2009; Luis Fuentes et al., 2020). Left atrial (LA) and aortic (Ao) dimensions were measured on the right parasternal short axial basilar view by M-mode echocardiography, and the LA/Ao ratio was calculated from these dimensions.

Left atrial dilatation was diagnosed when the left atrium-to-aorta (LA/Ao) ratio was >1.5 (Zimmering et al., 2010). Doppler echocardiography (color, pulse wave, and continuous) was performed to characterize flow disturbances and identify cases of HOCM also to calculate the ratio of peak early (E) diastolic to peak late (A) (Connolly et al., 2003; Schober et al., 2003; Fox et al., 2011). The RCM diagnostic criteria; are defined as cats with a restrictive mitral inflow Doppler pattern, biatrial or LA enlargement, and normal or mildly modified LV (Chetboul et al., 2019). Congestive heart failure (CHF) was diagnosed based on radiographic evidence of pulmonary edema or pleural effusion, presenting with dyspnea. We made the diagnosis of ATE with the presence of paralysis in the legs with the loss of peripheral pulse, limb cyanosis, cool extremities, and the presence of neuromuscular pain (Smith et al., 2003).

Samples collection and laboratory assays

All samples from cats were collected in serum tubes and tubes containing K3-EDTA, and lithium heparin by 21 g cannula. The serum obtained was separated within 20 minutes after coagulation. A portion of the serum was used to measure the sST2 level and stored at -80°C. The remaining samples were refrigerated before transportation to an outside laboratory (Vetlab

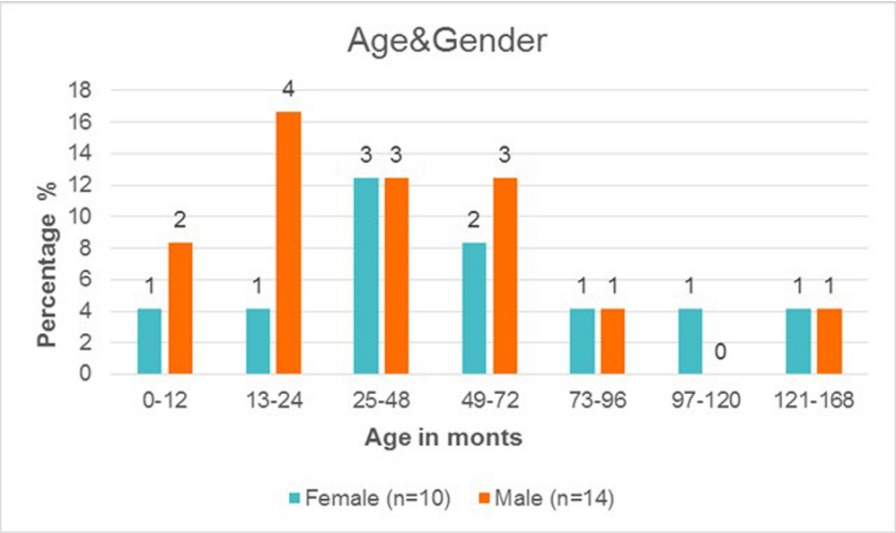

Figure 1: Age and gender distribution of the cats.

Veterinary Assay Laboratory, İstanbul, TURKEY) for determination of NT-proBNP, Troponin I, Troponin T, AST, LDH, and CK-MB levels. sST2 levels were measured by using a soluble interleukin 33 receptor ELISA kit (Bioassay Technology Laboratory, China). We used the quantitative sandwich ELISA method for the sST2 assessment of 4 standards and 21 serum samples with duplicates. The optical density of each ELISA well was determined by using an ELISA reader (Allsheng AMR-100 Microplate Reader, China) set to 450 nm.

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 13, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, USA). One-way ANOVA was used to compare the results of serum cardiac biomarkers, echocardiographic measurements of the left ventricle, and sST2 between the three groups. When ANOVA was significant, post hoc comparisons between groups were done using the Duncan test. Pearson's correlation was used to correlate serum levels of cardiac biomarkers and echocardiographic measurements of the left ventricle. Values of $P<0.05$ were considered to be statistically significant.

Results

Our cases consisted of five cats with HCM, one cat with HOCM, 11 cats with RCM, and five healthy control groups. The cats included in the study were 10 females and 14 males (Figure 1). Statistics for NT-proBNP, cTnI, cTnT, LDH concentrations and IVSd, LVFWd, LV EF%, LV FS%, Left atrial dimension (LAD), and LA/Ao ratio for the control and cardiomyopathy groups are summarized in Table 1. Serum sST2 levels were not significantly different between the healthy-control, symptomatic, and asymptomatic groups. The mean sST2 value of the healthy control group was 25.82 ng/mL (28.45-31.57 ng/mL), and the mean sST2 value of group I (Stage B1) was 24.47 ng/mL (15.38-35.67 ng/mL), while the mean sST2 value of the group II (Stage B2) was 24.47 ng/mL (13.25-30.55 ng/mL), and the mean sST2 value of the group III (Stage C) was 30.60 ng/mL (23.16- 38.55 mg/mL). All sST2 results in different groups are shown in Figure 2.

We observed positive correlations among sST2 levels and CK-MB and LAD ($p<0.05$). There was no correlation between sST2 and NT-proBNP, Troponin I, Troponin T, AST, and LDH levels. We confirmed positive correlations between NT-proBNP levels and LAD ($p<0.05$), CK-MB, IVSd, LVFWd, and LA/Ao ratio ($p<0.01$). A negative correlation between NT-proBNP levels and LVIDd ($p<0.05$) was found. Levels of cTnI were also positively correlated with cTnT ($p<0.05$), AST and LDH ($p<0.001$). cTnI levels were negatively correlated with LV FS% and LV EF% ($p<0.01$). cTnT levels were positively correlated with LAD ($p<0.05$). Positive correlations were detected between AST levels and LDH ($p<0.001$), and LVFWd ($p<0.05$). AST levels and LV EF ($p<0.05$), and LVFS ($p<0.05$) were also negatively correlated. LDH levels were positively correlated with LVFWd ($p<0.05$) and negatively correlated with LV EF% ($p<0.05$) and LV FS% ($p<0.05$). CK-MB showed a positive correlation with LA/Ao ratio ($p<0.05$) and LAD ($p<0.01$).

Among echocardiographic variables, IVSd was positively correlated with LAD ($p<0.05$), LVFWd ($p<0.001$), and LA/Ao ($p<0.001$), while negatively correlated with LVIDd ($p<0.05$). The LA/Ao ratio was positively correlated with LAD ($p<0.01$) and negatively correlated with LV EF% and LV FS% ($p<0.05$). LVFWd was positively correlated with LAD ($p<0.01$) and negatively correlated with LVIDd ($p<0.05$). LVIDd was positively correlated with LVIDs ($p<0.001$). In addition, LVIDs were negatively correlated with LV EF% and LV FS% ($p<0.01$). LV EF% and LV FS% ($p<0.001$) were positively correlated with each other.

Table 1: Biomarkers, echocardiographic, and doppler findings in cats with cardiomyopathies that divided into four classes according to ACVIM classification.

Variable*	All cats (n=24)	Group I (ACVIM stage B1) (n=7)	Group II (ACVIM stage B2) (n=6)	Group III (ACVIM stage C) (n=6)	Group IV (Healthy -control) (n=5)	P value
sST2	26.344±1.440	24.664±3.297[a]	24.473±2.624[a]	30.608±2.274[a]	25.824±2.958[a]	0.407
NT-proBNP	216.79±28.252	141.43±42.246[a]	348.00±48.280[b]	288.17±30.196[b]	79.20±1.800[a]	0.000
Troponin I	5.20±1.862	0.06±0.006[a]	5.03±2.191[a]	15.68±5.141[b]	0.04±0.003[a]	0.002
Troponin T	0.493±0.206	0.027±0.002[a]	0.151±0.069[a]	1.777±0.580[b]	0.016±0.001[a]	0.001
LDH	853.25±170.359	639.71±137.910[a]	770.33±176.632[ab]	1639.83±533.253[b]	307.80±98.618[a]	0.033
IVSd	7.542±0.299	7.429±0.347[b]	8.517±0.654[b]	8.233±0.416[b]	5.700±0.207[a]	0.002
LVFWd	7.925±0.405	7.914±0.301[b]	8.850±0.831[b]	9.133±0.777[b]	5.380±0.318[a]	0.002
LV EF%	76.100±2.881	83.043±3.734[a]	75.617±3.934[a]	60.683±5.723[b]	85.460±4.167[a]	0.000
LV FS%	46.042±2.464	52.043±4.543[a]	43.933±3.501[a]	34.967±3.597[b]	53.460±4.692[a]	0.004
LA diameter	14.542±0.670	14.286±0.872[ab]	14.383±1.708[ab]	17.483±0.875[b]	11.560±0.647[a]	0.019
LA/Ao	1.935±0.110	1.715±0.023[b]	2.283±0.203[c]	2.390±0.157[c]	1.278±0.107[a]	0.017

* Values are expressed as mean± standard error

[a,b] Superscript letters identify groups which differed significantly

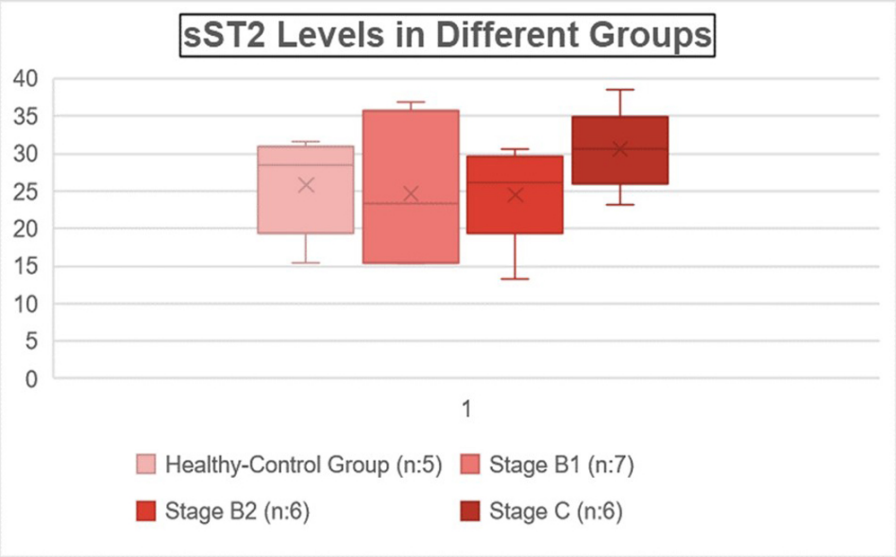

Figure 2: Comparison of sST2 levels between four groups.

Discussion

Echocardiography is the gold standard for identifying cats with cardiogenic respiratory distress, but it is not always applicable. Cats with respiratory distress are generally unstable and intolerant of handling or diagnostic interventions. Measurement of a cardiac biomarker may be helpful if a blood sample can be obtained with minimal stress, which might be safer than thoracic radiography and echocardiography.

The NT-proBNP and troponins are the most effective biomarkers to distinguish whether cat's respiratory distress is cardiogenic or non-cardiogenic (Sleeper et al., 2001; Connolly et al., 2008). However, our search for a new independent cardiac biomarker continues due to increased concentrations in conditions such as hyperthyroidism and kidney diseases. Previous studies have shown that using multiple biomarkers is more effective than using a single marker (Oyama et al., 2013).

ST2 *in-vivo* binds to IL33, which has antihypertrophic and antifibrotic effects on cardiomyocytes. In this way, sST2 may serve as an adverse "decoy receptor" for circulating IL-33, minimizing the protective effects of IL33 on the cardiovascular system (Sanada et al., 2007). Furthermore, in humans, the concentration of sST2 increases with the severity of heart disease, and increasing concentrations highly and independently predict one-year mortality (Boswood, 2009). This predictive value complemented Troponins and NT-proBNP, suggesting that a multi-biomarker strategy for risk stratification in human and veterinary medicine might be the best way forward.

This study was designed to evaluate a novel cardiac biomarker, sST2, as a potential predictor of the severity of cardiomyopathies in the feline. Recently, interest in cardiac biomarkers has increased, but to date, sST2 are scarce. The few available studies have focused on the evaluation of heart failure in dogs and have reported no difference in sST2 levels between

groups (Boswood, 2009; Oyama et al., 2013; Kim et al., 2018). In this study comparison of ST2 levels within the healthy-control, asymptomatic, and symptomatic cats with cardiomyopathies groups showed no significant difference among groups, and sST2 levels were positively correlated with CK-MB and LAD.

NT-proBNP levels in patients with HCM correlated positively with hypertrophy severity, left ventricular (LV) diastolic dysfunction, LV outflow tract gradient, death prediction, and heart failure-related events (Gawor et al., 2018). In a study, an NT-proBNP concentration of >95 pmol/L discriminated healthy cats from asymptomatic cats with cardiac enlargement (Wess et al., 2011). Another study found that an NT-proBNP concentration <100 pmol/L distinguished clinically normal cats from cats with HCM (Tominaga et al., 2011). When the NT-proBNP level is over 270 pmol/L, the risk of heart failure is a concern (Bakirel et al., 2021). In this study, the mean NT-proBNP level of the healthy control group was 79.20 pmol/L, class B1 141.43 pmol/L, and class B2 cats were 288.17 pmol/L. We confirm that in all cats and cats with HCM, the NT-proBNP concentration increased with increasing IVSd and LVFWd. In our study, the left ventricular hypertrophy and LA enlargement were associated with significantly increased NT-proBNP concentrations in cats with cardiomyopathies.

It has been reported that circulating cTnI concentrations are elevated in cats with HCM and higher cTnI concentrations have a poor prognosis (Langhorn et al., 2014; Hori et al., 2018). Many studies have shown that cTnI and cTnT are associated with cardiac death, and troponins provide useful prognostic information (Borgeat et al., 2014; Langhorn et al., 2014). In our study, significant differences in cTnI and cTnT levels were detected between the groups. The mean cTnI level of the healthy control group was 0.04 ng/mL, class B1 0.06 ng/mL, class B2 5.03 ng/mL, and class C cats were 15.68 ng/mL. In a previous study, cTnI >0.7 ng/mL was associated with a shorter survival time to cardiac death, but also it had a predictive value on the CHF and LAD. In our study, a positive correlation was found between LAD and cTnT.

The LA dilatation is one of the most important indicators of severity and poor outcome in cats with cardiomyopathies (Trehiou-Sechi et al., 2012). Another important finding of this study is a positive correlation between sST2 and LAD. In a recent study, sST2 levels correlated with the left atrial diameter and were more elevated in patients with a more persistent form of atrial fibrillation (Chen et al., 2018).

In conclusion, our data demonstrated that as the severity of cardiomyopathy increases, the levels of Nt-proBNP, cTnI, cTnT, and LDH increase, and the use of these biomarkers in feline cardiomyopathy had been reconfirmed. Another important finding in this study is that the positive correlation between sST2 and LAD may be important for cats with cardiomyopathy. However, these results could not confirm the single or multiple uses of sST2 with other biomarkers. Therefore, new studies with a larger patient population are needed.

Limitations

The main limitation of our study is the number of cats involved. Serial measurement of sST2 in human medicine is essential for risk classification and prognostication. Another limitation is that sST2 levels were not measured serially. A comparison of sST2 levels assessed with pre and post-treatment periods between similar groups may also be considered in future studies. In addition, our analysis includes different types of cardiomyopathy, but sST2 levels may differ between HCM, RCM, and HOCM.

Article Information

Funding. This research received no funds.

Conflict of Interest. The authors have no conflict of interest to declare.

References

Bakirel, U., Ulgen Saka, S., Yildiz, K., 2021. Feline arteriyel tromboembolizm tanısı ve prognozunda kardiyak biyobelirteçlerin rolü ve önemi. Kafkas Universitesi Veteriner Fakultesi Dergisi 10.9775/kvfd.2020.25073.

Biaggi, P., Ammann, C., Imperiali, M., Hammerer-Lercher, A., Breidthardt, T., Müller, C., Maisel, A., Ruschitzka, F., 2019. Soluble ST2: A new biomarker in heart failure. Cardiovascular Medicine 22. 10.4414/cvm.2019.02008.

Borgeat, K., Sherwood, K., Payne, J.R., Luis Fuentes, V., Connolly, D.J., 2014. Plasma cardiac troponin I concentration and cardiac death in cats with hypertrophic cardiomyopathy. Journal of Veterinary Internal Medicine 28, 1731–1737. 10.1111/jvim.12459.

Boswood, A., 2009. Biomarkers in cardiovascular disease: Beyond natriuretic peptides. Journal of Veterinary Cardiology 11 Suppl 1, S23–32. 10.1016/j.jvc.2009.01.003.

Chen, C., Qu, X., Gao, Z., Zheng, G., Wang, Y., Chen, X., Li, H., Huang, W., Zhou, H., 2018. Soluble ST2 in patients with nonvalvular atrial fibrillation and prediction of heart failure. International Heart Journal 59, 58–63. 10.1536/ihj.16-520.

Chetboul, V., Passavin, P., Trehiou-Sechi, E., Gouni, V., Poissonnier, C., Pouchelon, J.L., Desquilbet, L., 2019. Clinical, epidemiological and echocardiographic features and prognostic factors in cats with restrictive cardiomyopathy: A retrospective study of 92 cases (2001-2015). Journal of Veterinary Internal Medicine 33, 1222–1231. 10.1111/jvim.15464.

Connolly, D., Cannata, J., Boswood, A., Archer, J., Groves, E., Neiger, R., 2003. Cardiac troponin I in cats with hypertrophic cardiomyopathy. Journal of Feline Medicine and Surgery 5, 209–216. 10.1016/S1098-{612X}(03)00007-X.

Connolly, D.J., Magalhaes, R.J.S., Syme, H.M., Boswood, A., Fuentes, V.L., Chu, L., Metcalf, M., 2008. Circulating natriuretic peptides in cats with heart disease. Journal of Veterinary Internal Medicine 22, 96–105. 10.1111/j.1939-1676.2007.0024.x.

Elliott, P., Andersson, B., Arbustini, E., Bilinska, Z., Cecchi, F., Charron, P., Dubourg, O., Kühl, U., Maisch, B., McKenna, W.J., Monserrat, L., Pankuweit, S., Rapezzi, C., Seferovic, P., Tavazzi, L., Keren, A., 2008. Classification of the cardiomyopathies: A position statement from the european society of cardiology working group on myocardial and

pericardial diseases. European Heart Journal 29, 270–276. 10.1093/eurheartj/ehm342.

Ferasin, L., 2009. Feline myocardial disease. 1: Classification, pathophysiology and clinical presentation. Journal of Feline Medicine and Surgery 11, 3–13. 10.1016/j.jfms.2008.11.008.

Fox, P.R., Keene, B.W., Lamb, K., Schober, K.E., Chetboul, V., Luis Fuentes, V., Payne, J.R., Wess, G., Hogan, D.F., Abbott, J.A., Häggström, J., et al., 2019. Long-term incidence and risk of noncardiovascular and all-cause mortality in apparently healthy cats and cats with preclinical hypertrophic cardiomyopathy. Journal of Veterinary Internal Medicine 33, 2572–2586. 10.1111/jvim.15609.

Fox, P.R., Oyama, M.A., Reynolds, C., Rush, J.E., DeFrancesco, T.C., Keene, B.W., Atkins, C.E., Macdonald, K.A., Schober, K.E., Bonagura, J.D., Stepien, R.L., Kellihan, H.B., Nguyenba, T.P., Lehmkuhl, L.B., Lefbom, B.K., Moise, N.S., Hogan, D.F., 2009. Utility of plasma n-terminal pro-brain natriuretic peptide (NT-proBNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. Journal of Veterinary Cardiology 11 Suppl 1, S51–61. 10.1016/j.jvc.2008.12.001.

Fox, P.R., Rush, J.E., Reynolds, C.A., Defrancesco, T.C., Keene, B.W., Atkins, C.E., Gordon, S.G., Schober, K.E., Bonagura, J.D., Stepien, R.L., Kellihan, H.B., Macdonald, K.A., Lehmkuhl, L.B., Nguyenba, T.P., Sydney Moise, N., Lefbom, B.K., Hogan, D.F., Oyama, M.A., 2011. Multicenter evaluation of plasma n-terminal probrain natriuretic peptide (NT-pro BNP) as a biochemical screening test for asymptomatic (occult) cardiomyopathy in cats. Journal of Veterinary Internal Medicine 25, 1010–1016. 10.1111/j.1939-1676.2011.00776.x.

Gawor, M., Śpiewak, M., Kubik, A., Wróbel, A., Lutyńska, A., Marczak, M., Grzybowski, J., 2018. Circulating biomarkers of hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy assessed by cardiac magnetic resonance. Biomarkers: Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals 23, 676–682. 10.1080/1354750X.2018.1474261.

Hori, Y., Iguchi, M., Heishima, Y., Yamashita, Y., Nakamura, K., Hirakawa, A., Kitade, A., Ibaragi, T., Katagi, M., Sawada, T., Yuki, M., Kanno, N., Inaba, H., Isayama, N., Onodera, H., Iwasa, N., Kino, M., Narukawa, M., Uchida, S., 2018. Diagnostic utility of cardiac troponin I in cats with hypertrophic cardiomyopathy. Journal of Veterinary Internal Medicine 32, 922–929. 10.1111/jvim.15131.

Kim, J.K., Park, J.S., Seo, K.W., Song, K.H., 2018. Evaluation of ST2 and NT-proBNP as cardiac biomarkers in dogs with chronic mitral valve disease. Journal of Veterinary Clinics 35, 35–38. 10.17555/jvc.2018.04.35.2.35.

Lalor, S.M., Gunn-Moore, D.A., Cash, R., Foot, A., Reed, N., Mellanby, R.J., 2014. Serum cardiac troponin I concentrations in cats with anaemia: A preliminary, single-centre observational study. The Journal of Small Animal Practice 55, 320–322. 10.1111/jsap.12210.

Langhorn, R., Tarnow, I., Willesen, J.L., Kjelgaard-Hansen, M., Skovgaard, I.M., Koch, J., 2014. Cardiac troponin I and T as prognostic markers in cats with hypertrophic cardiomyopathy. Journal of Veterinary Internal Medicine 28, 1485–1491. 10.1111/jvim.12407.

Luis Fuentes, V., Abbott, J., Chetboul, V., Côté, E., Fox, P.R., Häggström, J., Kittleson, M.D., Schober, K., Stern, J.A., 2020. ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. Journal of Veterinary Internal Medicine 34, 1062–1077. 10.1111/jvim.15745.

Maron, B.J., Fox, P.R., 2015. Hypertrophic cardiomyopathy in man and cats. Journal of Veterinary Cardiology 17, S6–S9. 10.1016/j.jvc.2015.03.007.

Menaut, P., Connolly, D.J., Volk, A., Pace, C., Luis Fuentes, V., Elliott, J., Syme, H., 2012. Circulating natriuretic peptide concentrations in hyperthyroid cats. The Journal of Small Animal Practice 53, 673–678. 10.1111/j.1748-5827.2012.01301.x.

Oyama, M.A., Boswood, A., Connolly, D.J., Ettinger, S.J., Fox, P.R., Gordon, S.G., Rush, J.E., Sisson, D.D., Stepien, R.L., Wess, G., Zannad, F., 2013. Clinical usefulness of an assay for measurement of circulating N-terminal pro-B-type natriuretic peptide concentration in dogs and cats with heart disease. Journal of the American Veterinary Medical Association 243, 71–82. 10.2460/javma.243.1.71.

Sanada, S., Hakuno, D., Higgins, L.J., Schreiter, E.R., McKenzie, A.N.J., Lee, R.T., 2007. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. The Journal of Clinical Investigation 117, 1538–1549. 10.1172/JCI30634.

Sangster, J.K., Panciera, D.L., Abbott, J.A., Zimmerman, K.C., Lantis, A.C., 2014. Cardiac biomarkers in hyperthyroid cats. Journal of Veterinary Internal Medicine 28, 465–472. 10.1111/jvim.12259.

Schober, K.E., Fuentes, V.L., Bonagura, J.D., 2003. Comparison between invasive hemodynamic measurements and noninvasive assessment of left ventricular diastolic function by use of Doppler echocardiography in healthy anesthetized cats. American Journal of Veterinary Research 64, 93–103. 10.2460/ajvr.2003.64.93.

Singletary, G.E., Rush, J.E., Fox, P.R., Stepien, R.L., Oyama, M.A., 2012. Effect of NT-pro-BNP assay on accuracy and confidence of general practitioners in diagnosing heart failure or respiratory disease in cats with respiratory signs. Journal of Veterinary Internal Medicine 26, 542–546. 10.1111/j.1939-1676.2012.00916.x.

Sleeper, M.M., Clifford, C.A., Laster, L.L., 2001. Cardiac troponin i in the normal dog and cat. Journal of Veterinary Internal Medicine 15, 501. 10.1892/0891-6640(2001)015<0501:CTIITN<2.3.CO;2.

Smith, S.A., Tobias, A.H., Jacob, K.A., Fine, D.M., Grumbles, P.L., 2003. Arterial thromboembolism in cats: Acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases. Journal of Veterinary Internal Medicine 17, 73. 10.1892/0891-6640(2003)017<0073:ATICAC>2.3.CO;2.

Spalla, I., Locatelli, C., Riscazzi, G., Santagostino, S., Cremaschi, E., Brambilla, P., 2016. Survival in cats with primary and secondary cardiomyopathies. Journal of Feline Medicine and Surgery 18, 501–509. 10.1177/1098612X15588797.

Thomas, W.P., Gaber, C.E., Jacobs, G.J., Kaplan, P.M., Lombard, C.W., Moise, N.S., Moses, B.L., 1993. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee

of the Specialty of Cardiology, American College of Veterinary Internal Medicine. Journal of Veterinary Internal Medicine 7, 247–252. 10.1111/j.1939-1676.1993.tb01015.x.

Tominaga, Y., Miyagawa, Y., Toda, N., Takemura, N., 2011. The diagnostic significance of the plasma N-terminal pro-B-type natriuretic peptide concentration in asymptomatic cats with cardiac enlargement. The Journal of Veterinary Medical Science 73, 971–975. 10.1292/jvms.10-0303.

Trehiou-Sechi, E., Tissier, R., Gouni, V., Misbach, C., Petit, A.M.P., Balouka, D., Sampedrano, C.C., Castaignet, M., Pouchelon, J.L., Chetboul, V., 2012. Comparative echocardiographic and clinical features of hypertrophic cardiomyopathy in 5 breeds of cats: A retrospective analysis of 344 cases (2001-2011). Journal of Veterinary Internal Medicine 26, 532–541. 10.1111/j.1939-1676.2012.00906.x.

Wess, G., Daisenberger, P., Mahling, M., Hirschberger, J., Hartmann, K., 2011. Utility of measuring plasma N-terminal probrain natriuretic peptide in detecting hypertrophic cardiomyopathy and differentiating grades of severity in cats. Veterinary Clinical Pathology 40, 237–244. 10.1111/j.1939-165X.2011.00305.x.

Wood, M.J., Picard, M.H., 2004. Utility of echocardiography in the evaluation of individuals with cardiomyopathy. Heart 90, 707–712. 10.1136/hrt.2003.024778.

Zimmering, T.M., Hungerbühler, S., Meneses, F., Nolte, I., Simon, D., 2010. Evaluation of the association between plasma concentration of N-terminal proatrial natriuretic peptide and outcome in cats with cardiomyopathy. Journal of the American Veterinary Medical Association 237, 665–672. 10.2460/javma.237.6.665.