Hobbes' Hyped Up Heart

A Case Report of Feline Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy is a myocardial disease characterized by increased left ventricular wall thickness. This can manifest as diffuse hypertrophy (symmetrical and concentric), asymmetrical hypertrophy affecting the interventricular septum or left ventricular free wall, or as solitary segments in the left ventricle including the papillary muscle.[14]Primary hypertrophic cardiomyopathy is a genetic condition caused by a sarcomeric gene mutation that occurs in the absence of secondary causes such as systemic illness or cardiac disease.[4,15] This disease process is ultimately a diagnosis of exclusion. An autosomal dominant heritability component has been found in the Ragdoll and Maine Coon breeds.[4] Mutations involving the *MYBPC3* sarcomeric protein-encoding gene have been associated with an early onset of clinical signs and poor prognosis. [1]The mutation affecting the Ragdoll breed occurring at *MYBPC3 R820W* has a prevalence of 17-30% within the population.[1]Maine Coon cats have a similar mutation but occurring at a different locus *MYBPC3 A31P* with a prevalence of 34% affecting the breed.[12] Secondary cardiomyopathy causes that should be ruled out include, but are not limited to, systemic hypertension, hyperthyroidism, acromegaly, neoplasia, subaortic stenosis, pseudohypertrophy due to dehydration, *Bartonella henselae,* and transient myocardial thickening.

The prevalence of hypertrophic cardiomyopathy in healthy young cats is low at approximately <5% but does steadily increase with age.[4] Apparent hypertrophic cardiomyopathy is most frequently diagnosed in middle-aged (mean age 6 years) male cats, but clinical signs can occur at any age.[11,15] Most cats with hypertrophic cardiomyopathy remain asymptomatic and undergo a relatively benign clinical course throughout their lifetime.[4]However, as the age of the cat increases, they become more at risk of developing congestive heart failure, aortic

thromboembolism, and sudden cardiac death.[2]Left atrial size and age (i.e., older cats) have consistently been proven in studies to be negatively correlated with survival time. [11]Depending on the stage and severity of disease, clinical signs may be subtle and include: weight loss, anorexia, lethargy, tachypnea and dyspnea. If a cat presents tachypneic or dyspneic, this may be indicative of congestive heart failure. There are several factors that influence the highly variable prognosis for cats with hypertrophic cardiomyopathy, including whether signs of congestive heart failure are present at the time of diagnosis. Nevertheless, treatment goals for the disease process are achieved using both pharmacologic and nonpharmacologic management strategies.

History and Presentation

Hobbes, an approximately 7-month-old, neutered male domestic shorthair feline, first presented to the MSU-CVM Emergency Service on July 21, 2019 for tachypnea, dyspnea, cyanotic mucous membranes, and inappetence. Hobbes was neutered and forelimb declawed four days prior on July 17, 2019, at his primary veterinarian and was discharged same day with no complications reported. The following day, Hobbes was administered ampicillin suspension and Onsior that was prescribed following his surgical procedures. On July 20, 2019, owners began to notice a change in Hobbes' breathing and took him to his primary veterinarian that evening where a dexamethasone injection was administered and Onsior discontinued. Hobbes was still eating and drinking normally up until the following morning on July 21st, when he became inappetent, and his owners noted his progressive tachypnea and cyanotic mucous membranes. Hobbes is an indoor-only cat that shares the household with a 2-year-old domestic shorthair and is up-to-date on vaccinations and is administered a flea/tick preventative.

On presentation to MSU-CVM, Hobbes was bright, alert, and responsive. Hobbes was noted to be tachypneic with a respiration rate of 92 breaths per minute. He had a pulse of 180

beats per minute and temperature of 102.3 degrees Fahrenheit. He was evaluated to have a body condition score of 4/9. He had pale pink mucous membranes with a capillary refill time of less than 2 seconds. He was estimated to be approximately 5% dehydrated based on skin turgor. On cardiac auscultation, a gallop rhythm was noted as well as a transient grade 2/6 parasternal focal heart murmur. The remainder of his physical exam was within normal limits. Hobbes was placed in an oxygen cage overnight and monitored closely for signs of respiratory distress.

Diagnostic Approach/Considerations

Several diagnostics were performed initially to determine the underlying etiology for Hobbes' respiratory signs. A minimum database, which included a complete blood count and serum chemistry, revealed a mild hyperphosphatemia and mild increase in ALP and CK values. Unfortunately, the complete blood count was not able to be interpreted due to clotting and was not resubmitted due to Hobbes' fractious temperament when handled for blood draw. An electrocardiogram showed a sinus tachycardia with no additional abnormalities. Thoracic radiographs revealed the following abnormalities: mild mediastinal shift to the right and a moderate, diffuse, unstructured interstitial to coalescing alveolar pulmonary pattern most severe in the left caudal lung lobe, most consistent with pulmonary edema. In addition, an enlarged cardiac silhouette characterized by dorsal deviation of the trachea and the cardiac silhouette spanning greater than 50% of the width of the thorax on ventral dorsal projection was noted. Due to the enlarged cardiac silhouette findings on radiographs, an echocardiogram was pursued. The left ventricular free wall and interventricular septum were asymmetrically thickened. Portions of the interventricular septum were hyperechoic and heterogeneous likely due to fibrosis and infarction. There was insufficiency of the mitral valve characterized by a large regurgitant jet. Narrowing of the left ventricular outflow tract was noted and likely due to the systolic anterior

motion of the mitral valve. Based on these echocardiogram results, there was a high consideration for hypertrophic cardiomyopathy and a consultation with a cardiologist was performed. Consultation findings revealed the following results: the mitral valve showed systolic anterior motion of the septal leaflet, no significant left atrial enlargement, left ventricular dimensions and contractility, moderate asymmetric left ventricular hypertrophy primarily affecting the left ventricular free wall, and mild mitral regurgitation. The final diagnosis based on echocardiogram was irregular left ventricular hypertrophy. These specific changes are typically most consistent with hypertrophic cardiomyopathy. However, the cardiologist's assessment of the clinical findings was that Hobbes' cardiomyopathy was very atypical and possibly due to something other than, but similar to, classic hypertrophic cardiomyopathy. Specifically, there were radiographic evidence and clinical signs consistent with congestive heart failure, but with normal left atrial size. The majority of cats with spontaneous congestive heart failure will have moderate to severe left atrial enlargement. In addition, given Hobbes' young age, transient myocardial thickening needed to be considered. Cardiac troponin 1 testing was recommended and found to be 0.203 ng/mL by the Ultra-Sensitive Troponin 1 Fasting test. Recent studies have found median troponin 1 concentration levels in healthy cats to range from 0.012-0.048 ng/mL.[5,6] Cardiac troponin plays a regulatory role in cardiomyocyte contraction.[6] Cardiac troponins circulate and serve as sensitive markers to myocardial injury. A study performed evaluated the sensitivity of cardiac troponin 1 as a screening test for hypertrophic cardiomyopathy and found a cutoff of 0.06 ng/mL provided good distinction between healthy cats and those affected with hypertrophic cardiomyopathy (sensitivity, 91.7%; specificity, 95.4%).[5] Pro-brain natriuretic peptide (NT-proBNP) is produced by cardiomyocytes in response to myocardial stretch as well as increased volume and pressure, and is therefore less sensitive in cases of hypertrophic

cardiomyopathy.[5] NT-proBNP also serves as a cardiac biomarker and is available for testing, but was not pursued in Hobbes' case since it is found to be less sensitive.[5] Based on the interpretation of Hobbes' diagnostic results, a definitive diagnosis could not be reached. However, transient myocardial thickening causing a secondary hypertrophic cardiomyopathy or primary hypertrophic cardiomyopathy were of highest suspicion, and an underlying myocarditis could not be ruled out.

Pathophysiology

Hypertrophic cardiomyopathy is the most commonly diagnosed cardiomyopathy in cats.[12] It is defined as hypertrophy of the left ventricle. Primary hypertrophic cardiomyopathy occurs without identifiable underlying causes and is a diagnosis of exclusion. An abnormal sarcomere defect is thought to activate myocyte dysfunction and disrupt cell signaling processes that ultimately leads to myocyte hypertrophy and abnormal myofiber arrangement, leading to concentric hypertrophy and decreased diastolic filling, with an increased heart rate as a compensatory mechanism.[2,11]Tachycardia increases myocardial oxygen requirements and contributes to ischemia by reducing diastolic perfusion time.[11] Concentric thickening of the left ventricle and interventricular septum are most characteristic of the disease process and can occur symmetrically or asymmetrically.[11] Myocardium hypertrophy and disarray contribute to ventricular wall stiffness and reduced ventricular distensibility promoting diastolic dysfunction with impaired ventricular filling, and an increase in diastolic pressure.[11] High ventricular pressure progresses to left atrial enlargement, which in turn causes an increase in pulmonary venous pressures. This cascade ultimately leads to congestive heart failure and pulmonary edema. Additionally, cats diagnosed with hypertrophic cardiomyopathy are at an increased risk of aortic thromboembolism due to left atrial enlargement and blood stasis.[2] Focal or diffuse areas

of myocardium or endocardium are remodeled and replaced with fibrosis as a consequence of increased heart rate and oxygen demand. Narrowed intramural coronary arteries may contribute to ischemia- associated fibrosis. Ischemia can incite arrhythmias, sudden death and possibly thoracic pain.[11] It's estimated that approximately 1/3 of cats affected with hypertrophic cardiomyopathy will have dynamic left ventricular outflow tract obstruction due to systolic anterior motion (SAM) of the anterior mitral valve leaflet.[4] This is caused by left ventricular papillary muscle hypertrophy, that leads to the anterior mitral valve leaflet causing obstruction of the left ventricle outflow tract. Hypertrophy of the interventricular septum can contribute to the dynamic obstruction.[11]

Cases of secondary cardiomyopathy mimic hypertrophic cardiomyopathy by causing an increase in left ventricular wall thickness, such as occurs with transient myocardial thickening. However, the increased ventricular thickness in the latter is not due to myocyte hypertrophy or hyperplasia, but rather myocardial edema and/or transient cellular infiltration with the exact pathophysiology currently unknown.[10] A recent study found cats with transient myocardial thickening were younger than cats with hypertrophic cardiomyopathy (median age 1.7 vs. 8 years), and that the changes would often follow an antecedent event, such as anesthesia within days of onset of clinical signs.[10] Transient myocardial thickening can cause congestive heart failure, and therefore, similar clinical signs as hypertrophic cardiomyopathy, making differentiation on presentation difficult.[10] However, those cats affected with transient myocardial thickening had a better prognosis than expected for a cat with hypertrophic cardiomyopathy and associated congestive heart failure, which tends to have a poor prognosis.[10] It's speculated that transient myocardial thickening may be a form of myocarditis frequently described in people.[10] Infectious etiologies causing an acute myocarditis such as *Toxoplasma*, FIV, and *Bartonella* have

been described in literature.[10] A recent report details the diagnosis of transient myocardial thickening in a 3-year-old *Bartonella henselae* positive cat that had complete resolution of signs with appropriate treatment.[8]

Diagnosis

Differentiation of hypertrophic cardiomyopathy from other disorders is best achieved by echocardiography. Echocardiography allows for the assessment of hypertrophy and distribution affecting the ventricular wall, septum, and/or papillary muscles.[11] An end-diastolic left ventricular wall or septal wall thickness greater than 5.5 to 5.9 mm is considered abnormal.[11] It's important to note that the degree of hypertrophy does not necessarily equate to the severity of clinical signs.[11] In cases of hypertrophic cardiomyopathy, myocardial wall thickness is due to myocyte hypertrophy.[10] Transient myocardial thickening is not caused by myocyte hypertrophy, but rather, interstitial infiltration of proteins, cells or fluid.[10] However, there is typically no clinical or echocardiographic evidence to differentiate the two disease processes at presentation. Differentiation between hypertrophic cardiomyopathy and endocrine disease processes, can however, be made via diagnostic testing. A complete blood count, serum chemistry, T4, cardiac troponin 1, FeLV/FIV, and possible *Bartonella* and *Toxoplasma* testing are recommended to rule out secondary hypertrophic cardiomyopathy and guide future treatment.

Treatment and Management

Treatment for hypertrophic cardiomyopathy can be subdivided into three categories based on clinical findings. Treatment should be based on a subclinical, clinical, or chronic refractory hypertrophic cardiomyopathy. Appropriate diagnostic testing should be performed prior to treatment to exclude secondary causes of left ventricular hypertrophy. Treatment management for cats determined to be subclinical is of some controversy, with no general consensus.

Currently, there is no proven treatment to delay the progression of congestive heart failure, aortic thromboembolism, and sudden cardiac death.[4] A number of small studies using a ß-blocker, diltiazem, and angiotensin-converting enzyme (ACE) inhibitor have been performed, but no clear benefit has been shown.[11]Administration of a ß-blocker, such as atenolol, in cats with evidence of significant dynamic left ventricular outflow tract obstruction is suggested to decrease heart rate and lessen the possible effects of myocardial ischemia.[4] The effect of treatment with atenolol over a 5-year span was studied in cats with subclinical hypertrophic cardiomyopathy. This study found no significant difference in survival between cats treated or untreated with atenolol.[13]Another study performed found atenolol therapy effectively decreased heart rate, murmur grade, and left ventricular outflow obstruction in cats subclinical for hypertrophic cardiomyopathy.[7] However, a prolonged time to onset of heart failure or improved long-term outcome with atenolol therapy was not evaluated in this study. An ACE inhibitor or diltiazem may be indicated in cases of marked, nonobstructive myocardial hypertrophy.[11] In addition, with cases of left atrial enlargement, antithrombotic prophylaxis is particularly important and recommended. However, if there is an absence of extreme hypertrophy or left ventricular outflow tract obstruction and normal left atrial size, no treatment is generally indicated.[4] It's important to keep in mind that medicating a cat can have a significant impact on the quality of life of the owner and cat.[4] This must be considered when initiating treatment in low-risk cats.

Goals in the treatment of clinically evident hypertrophic cardiomyopathy consist of enhancing ventricular filling, minimizing ischemia, controlling arrhythmias, mitigating congestion, and preventing aortic thromboembolism.[11] Typically, furosemide is used to control signs of congestion and is the drug of choice for treating cardiogenic pulmonary edema in cases of congestive heart failure.[4] However, in cases of moderate to severe pleural effusion, treatment

with thoracocentesis is indicated.[11]An ACE inhibitor (enalapril or benazepril) is started when oral medications are able to be administered and the patient is hemodynamically stable.[3]A more recent study evaluated the use of benazepril in cats with heart disease which included hypertrophic cardiomyopathy, as well as, dilated cardiomyopathy, restrictive cardiomyopathy, unclassified cardiomyopathy, and valvular disease. The study found no beneficial effect of benazepril on the development of treatment failure defined in the study.[9] Benazepril, was however, found to be well tolerated and no adverse effects were reported within the study.[9]As previously mentioned, a ß-blocker or diltiazem can be used in cases of severe left ventricular hypertrophy to decrease heart rate and dynamic left ventricular outflow obstruction. ß-blockers are likely to decrease heart rate and left ventricular outflow obstruction to a greater extent than diltiazem.[11]However, ß-blockers are not recommended in cases of active congestive heart failure and can be associated with a poorer prognosis due to its negative effects on contractility or airway ß2-receptor antagonism in asthmatics.[11] Restricting dietary sodium and exercise is recommended. Sodium restriction should only be incorporated into the diet if the cat is willing to eat such a diet.[11]

Chronic refractory congestive heart failure can be difficult to manage in cases of hypertrophic cardiomyopathy. Spironolactone is a potassium-sparing diuretic that can be used in conjunction with furosemide in cases of refractory pulmonary edema or pleural effusion.[3] Pimobendan can be added in refractory cases as well, and may improve left atrial function.[15] It can be useful especially in cases where there is evidence of decreased left ventricular systolic function.[3] Pimobendan should, however, be used cautiously in cases with systolic anterior motion of the mitral valve. The effects of the inodilator drug have potential to worsen systolic anterior motion of the mitral valve and cats may develop significant hypotension.[3,15] Overall, several

factors influence the prognosis for cats diagnosed with hypertrophic cardiomyopathy.[11] The speed at which the disease progresses, as well as the development of arrhythmias and/or thromboembolic events and response to treatment are all factors that can significantly influence prognosis.[11] Cats diagnosed with mild, nonprogressive hypertrophic cardiomyopathy and no clinical signs have a median survival time of >5 years.[2] Young cats with severe left ventricular hypertrophy often progress and die more quickly, typically prior to 4 years of age.[2] Cases of severe hypertrophic cardiomyopathy with congestive heart failure have a poor long-term prognosis and median survival time of 3 months.[2] However, it's important to keep in mind that these times are highly variable and dependent on the individual patient. Hypertrophic cardiomyopathy and aortic thromboembolism have a poor prognosis, and recurrence of thromboembolism is common.[11]

Case Outcome

Hobbes remained in an oxygen cage from the day of presentation on July 21, 2019, to the morning of July 24, 2019. Hobbes' respiratory rate improved to around 40 breaths per minute within the oxygen cage. Thoracic radiographs were performed on July 21st, and Hobbes was transferred to the internal medicine service the morning of July 22nd. He was started on LRS fluid therapy once an IV catheter could be placed, since his fractious nature and unstable respiratory status prevented this at presentation. Given the suspicion of pulmonary edema on thoracic radiographs, furosemide (2mg/kg) was administered intravenously every 8 hours. Since Hobbes was recently anesthetized and began showing respiratory signs shortly after, clindamycin (12.5mg/kg) was also administered intravenously for potential aspiration pneumonia until further diagnostics could be performed. Gabapentin (100mg) was also administered orally every 12 hours to reduce anxiety. An echocardiogram was performed on July 23rd, and the findings were

sent to a cardiologist for consultation. Hobbes was administered alfaxalone prior to his echocardiogram, and did become minimally responsive for several minutes following administration. He was taken to the intensive care unit and recovered uneventfully and was later sedated with butorphanol to finish the echocardiogram. Hobbes remained stable in the intensive care unit with no episodes of respiratory distress reported. Hobbes' treatment plan was adjusted based on echocardiogram findings and recommendations from the cardiologist. IV fluids were discontinued. Furosemide dose was decreased to 1mg/kg intravenously every 12 hours, and benazepril (1.25mg/kg) was initiated and administered every 24 hours.

Hobbes was discharged on July 24, 2019 and was stable at the time of discharge. He was discharged with furosemide (1.2mg/kg) to be given orally every 12 hours, and benazepril (1.25mg/kg) to be given orally every 24 hours. Hobbes was discharged with instructions to return in one week to recheck renal values following initiation of benazepril. In addition, a recheck echocardiogram was to be scheduled in four weeks.

Unfortunately, Hobbes never returned for his recheck examinations and was lost to follow-up. A recent conversation with Hobbes' primary care hospital revealed limited but valuable information. Hobbes returned to the primary veterinarian on August 19, 2019, and at this time he was found to be doing well. His furosemide dose was decreased to every 24 hours. Hobbes hasn't been examined since August, but the owner did request a refill of benazepril in September 2019 and Bravecto in January 2020. It can be concluded based on this information that Hobbes has been doing well at home with no respiratory concerns. Ultimately, a recheck echocardiogram would be required to definitely diagnose Hobbes' condition. However, given that Hobbes has presumptively done well at home this information can further support a diagnosis of transient myocardial thickening, instead of hypertrophic cardiomyopathy.

Theoretically, if an echocardiogram were to be performed, cases of transient myocardial thickening would likely show a significant decrease in left ventricular wall thickness and possible complete resolution.[10] Transient myocardial thickening seems to preferentially affect young cats and often follows a prior event.[10] This case highlights the need to consider transient myocardial thickening in cases presenting with historically “classic” clinical signs of hypertrophic cardiomyopathy.

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