Hypertrophic Cardiomyopathy - Pathophysiology

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United States
Feline Hypertrophic Cardiomyopathy
Getting Into The Thick Of It

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DEFINITION
Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease that primarily affects left ventricular (LV) myocardium and is characterized by mild to severe thickening (concentric hypertrophy) of the LV wall (septum and/or free wall) and papillary muscles. The thickening may be global or regional. In feline HCM, the LV papillary muscles are consistently enlarged. The diagnosis is, to some degree, one of exclusion. Several possible secondary causes of LV concentric hypertrophy exist in cats including systemic arterial hypertension, hyperthyroidism and aortic stenosis. When LV hypertrophy is caused by any of these diseases, the cardiac abnormality is not called HCM since it is not cardiomyopathy (primary heart muscle disease). Instead it is called concentric hypertrophy secondary to the primary abnormality (e.g., concentric hypertrophy secondary to hyperthyroidism). However, it should be noted that no other primary or secondary cause of LV hypertrophy can generally increase the LV wall thickness to more than 1.5 times the upper limit of normal thickness. Consequently, when the LV wall is 7 mm thick or more in a cat, this is almost invariably severe HCM. The one possible exception to this rule is lymphoma, a rare cause of increased LV wall thickness produced by infiltration of the myocardium.

NOMENCLATURE
According to a recent American College of Cardiology/European Society of Cardiology Clinical Expert Consensus document, “HCM is now widely accepted as the preferred term because it describes the overall disease spectrum without introducing misleading inferences that LV outflow tract (LVOT) obstruction is an invariable feature of the disease, such as is the case with hypertrophic obstructive cardiomyopathy (HOCM), muscular subaortic stenosis, or idiopathic hypertrophic subaortic stenosis. Indeed, most patients with HCM do not demonstrate outflow obstruction under resting (basal) conditions, although many may develop dynamic subaortic gradients of varying magnitude with provocative maneuvers or agents.” It is suggested by the presenter that veterinary medicine should follow suit on this recommendation.

CLINICAL MANIFESTATIONS
Sex Predilection - A male predilection for HCM is commonly reported. However, in cat breeds where the mode of inheritance is known to be autosomal dominant (i.e., Maine Coon and Ragdoll cats) the incidence of the mutation is obviously the same in males and females. However, in Maine Coon cats it is known that males often develop a more severe form of the disease and do so at an earlier age than females. Consequently, it is likely that the male predominance seen clinically is purely because males develop worse disease and so present to a veterinarian.

Breed Predilection – The genetic cause of HCM in Maine Coon cats and Ragdoll cats has been determined and will be discussed in detail in a subsequent lecture. Numerous other breeds also have HCM as a prevalent problem, including, but not limited to, Persians, American and British Shorthairs, Siberians, Norwegian Forest Cats, and Turkish Vans. Most HCM is diagnosed in mixed breed cats (domestic shorthair, domestic longhair). The mutations identified so far in cats are inherited as autosomal dominant traits since they alter structural proteins and almost all mutations in humans are inherited in an autosomal dominant fashion. Given the breeding patterns of domestic cats, it is not difficult to see how an autosomal dominant trait could disseminate into the population at large. It may also be that the portions of the feline genome that are responsible for sarcomere development are more prone to mutation than other species.

Natural History - HCM is a progressive disease in Maine coon cats, as it is in humans. Although most cats with HCM are not or have not been followed over long periods like Maine Coon cats have, the disease is almost certainly progressive in other cats as well. In Maine Coon cats a typical scenario is for a cat to have no evidence of HCM during the first 2-3 years of life and then to develop
the maximum stage of its HCM (mild to severe HCM) after that. However, the course of progression is highly variable from cat to cat. Cats that only develop mild to moderate HCM usually have no clinical sequelae to their disease (although a small percentage may die suddenly). This means that it is possible that when a veterinarian examines an older cat and identifies, for example, moderate HCM, the disease has been present for much of the cat’s life. Cats that develop severe disease may go on to have severe sequelae (i.e., heart failure, sudden death, systemic thromboembolism) within a short period while others may stabilize for a remarkably long time. It would appear, and it would be logical, that cats that are homozygous for a mutation that causes HCM have an accelerated course to their disease and so have echocardiographic evidence of HCM at an earlier age and more frequently develop severe disease, again at an earlier age.

**History and Clinical Signs** - Cats with HCM may have no clinical evidence of the disease, many have a heart murmur, a few have a gallop sound (if the disease is severe), some are presented to a veterinarian with subtle signs of heart failure, others have moderate to severe heart failure and so tachypnea and/or dyspnea, and some are presented because of systemic thromboembolic disease. Cats with no clinical signs can have mild to severe left ventricular thickening, however, those with severe thickening usually go on to develop heart failure. Cats with severe disease that appear to have no clinical signs may show subtle signs of heart failure (e.g., tachypnea) that may be detected by an observant owner but more often goes undetected. The respiratory rate is often increased in these cats at rest or when asleep and they may become more tachypneic or even dyspneic if stressed. Cats with mild to moderate HCM may never develop clinical signs and may live normal lives. In others, the left ventricular wall may thicken further and complications may develop when they are older and develop a complicating disease such as systemic hypertension or hyperthyroidism. Cats with severe HCM and moderate to severe heart failure are most commonly presented to a veterinarian because of respiratory abnormalities (tachypnea and/or dyspnea) due to pulmonary edema, pleural effusion, or both. Since household cats are generally sedentary, owners usually do not notice that they are having respiratory difficulty until it is advanced. At that time, the onset of the disease commonly appears to be acute to the owner, whereas the disease actually has been present for years and the heart failure gradually worsening for weeks to months.

Cats with HCM may die suddenly, often with no prior clinical signs referable to heart disease or failure. The cause of the sudden death in these cats is unknown but may be due to a fatal arrhythmia, large thrombus lodging in the left ventricle or proximal aorta, or acutely worsening outflow tract obstruction associated with severe stress. The incidence of sudden death in feline HCM is probably underrepresented in the literature because cats that die suddenly are generally not presented or reported to veterinarians.

**Physical Examination** - Cats with severe HCM commonly have auscultatory abnormalities. A systolic murmur, heard best over the mid sternum or left apex beat is common and is usually due to SAM. The murmur is often dynamic, increasing in intensity when the cat becomes excited and heart rate and myocardial contractility increase (especially when contractility of the papillary muscles increases) and decreasing in intensity or disappearing when the cat is calm. It should be noted that change in contractility, not heart rate, is the cause of the change in murmur intensity. Heart rate change is just along for the ride and is an index of changes in sympathetic tone.

A gallop sound may be present in cats with severe HCM. It should be noted that not all three-heart-sound rhythms are due to gallop sounds since systolic clicks also occur with some frequency in cats. A systolic click is more likely to vary in intensity (although often it does not) and should be the assumed cause when there is mild or no apparent cardiac disease present.

**PATHOPHYSIOLOGY**

HCM almost always causes diastolic dysfunction rather than systolic dysfunction. Diastolic dysfunction is usually either a problem with chamber compliance (stiffness) or chamber relaxation. Severe concentric hypertrophy by itself increases chamber stiffness. In addition, blood flow and especially blood flow reserve to severely thickened myocardium is compromised which causes myocardial ischemia, cell death, and replacement fibrosis. This has been documented in cats by showing that cardiac troponin I concentration is increased in cats with severe HCM. Increased concentrations of circulating neurohormones may also stimulate the production of collagen, which produces interstitial fibrosis. Fibrosis increases chamber stiffness (increased ∆pressure/∆volume) further and is the primary reason for the marked diastolic dysfunction seen in this disease. The stiff ventricular chamber causes a greater increase in pressure for any given increase in volume when the
ventricle fills in diastole. The increased diastolic pressure backs up into the left atrium, pulmonary veins and pulmonary capillaries and produces congestive heart failure (CHF) (i.e., pulmonary edema and pleural effusion).

When LV hypertrophy is severe, it is common for the LV wall thickness to be twice the normal thickness (increased from 3-5 mm up to 7-10 mm). The end-systolic volume and diameter are almost always reduced, often to zero (end-systolic cavity obliteration). Studies in humans have shown that global myocardial contractility is normal in patients with HCM and so is not the cause of the decreased end-systolic volume. Instead the reduction in end-systolic volume is due to a decrease in afterload (systolic wall stress) brought on by the increase in wall thickness (explained by Laplace’s law).

Left heart failure is manifested as either pulmonary edema or pleural effusion in cats. The pleural effusion is thought to be produced from the surface of the lungs since the visceral pleural veins drain into pulmonary veins (and so the left heart). Of course, pleural effusion can also be produced by right heart failure since the parietal pleura (pleura lining the chest cavity) drains into the systemic venous system but in the vast majority of cats with heart failure due to HCM there is absolutely no evidence of right heart failure (e.g., an enlarged right atrium, jugular or hepatic vein distension).

**Systolic Anterior Motion (SAM) of the Mitral Valve** - SAM of the mitral valve is common in cats with HCM. Cats with HCM and SAM are commonly said to have the obstructive form of HCM or hypertrophic obstructive cardiomyopathy (HOCM). In one survey of 46 cats, SAM was present in 67%. However, as in humans, SAM comes and goes depending on thecontractile state of the heart so it is likely that SAM can be provoked in many cats that do not have SAM at rest by just taking them to see a veterinarian and it is also likely that many cats that have SAM in a veterinary clinic do not have it when they are home and asleep. As noted previously, it has been recommended that the term HOCM be dropped.

Systolic anterior motion of the mitral valve is the process of the septal (anterior) mitral valve leaflet or the chordal structures inserting on this leaflet being pulled into the LVOT during systole by the enlarged papillary muscles. Here it is caught in the blood flow and pushed toward and often ultimately against the interventricular septum. The initial pulling of the mitral valve leaflet toward the LVOT in systole can clearly be seen on many echocardiograms from cats with HCM to be due to the grossly enlarged papillary muscles encroaching on the LVOT (the region of the LV between the anterior leaflet of the mitral valve and the interventricular septum) and pulling the mitral apparatus structures into the basilar region of the outflow tract. SAM produces a dynamic subaortic stenosis that increases the velocity of blood flow through the subaortic region and usually produces turbulence. Simultaneously, when the septal leaflet is pulled toward the interventricular septum, a gap in the mitral valve is produced creating mitral regurgitation. These abnormalities are by far the most common causes of the heart murmur heard in cats with HCM.

**PATHOLOGY**

**Gross Pathology** - Cats with severe HCM have severe thickening of the LV myocardium (the interventricular septum and free wall), with the LV wall measuring 7-10 mm thick. The hypertrophy may be symmetric, involving the entire circumference of the LV, but is often asymmetric. In some cats the interventricular septum is significantly thicker than the free wall while in others the free wall is thicker (asymmetric hypertrophy). In those cats with primarily septal hypertrophy the hypertrophy most commonly involves the entire septum but it may be confined to the basilar or apical regions of the septum. Isolated free wall hypertrophy most commonly occurs in the region between the papillary muscles.

As in many pathologic specimens, hearts from cats with HCM may undergo contraction (rigor) following death resulting in a wall thickness that is closer to the end-systolic wall thickness in life rather than the end-diastolic thickness (falsely thickened). Consequently, heart weight must be combined with subjective or objective evidence of LV wall thickening to make the diagnosis of HCM post mortem. To weigh a cat heart the pericardium should be removed and the aorta and pulmonary artery transected so that no more than 2-4 cm are left. Most normal cats have a heart that weighs less than 20 gm and so most cats with HCM have a heart that weighs more than 20 grams. Cats with severe HCM almost always have a heart that weighs more than 25 gm, usually weigh over 30 gm, and can be as heavy as 38 gm.

The left atrium is always enlarged in cats with HCM that are in heart failure. The left atrium, however is not always enlarged in cats with HCM. Even with early, severe disease we have identified
normal left atrial size in some Maine Coon cats. Occasionally a thrombus is present, most commonly within the left auricle. Cats with mild to moderate HCM have lesser wall thickening and a more normal sized LV chamber. The left atrium is usually normal in size but may be enlarged. Papillary muscle hypertrophy is often the predominant lesion.

**Histopathology** - Histopathologically, there is a wide range of abnormalities from only myocyte hypertrophy to moderate to severe interstitial and replacement fibrosis and dystrophic mineralization (20 to 40% of cases). In humans, myocardial fiber disarray (MFD) that involves at least 5% of the myocardium in the interventricular septum is found in 90% of patients with familial HCM. In cats with HCM, myocardial fiber disarray in the interventricular septum of the same magnitude observed in humans is only identified in 30% to 60% of cases. However, myocardial fiber disarray is a consistent feature of HCM in Maine coon cats. Unfortunately, most veterinary pathologists are not trained to characterize MFD.

**DIAGNOSIS**

**Echocardiography** - The diagnosis of HCM is almost always made using echocardiography where cats with severe HCM have severe papillary muscle hypertrophy, a markedly thickened LV wall (7-10 mm), and often, but certainly not always, an enlarged left atrium. The hypertrophy can be global, affecting all areas of the LV wall or can be more regional. Because it can be regional, HCM is a diagnosis that should be made by examining several different two-dimensional echocardiographic views and measuring wall thickness in diastole from the thickest region or regions. M-mode echocardiography may miss regional thickening unless it is guided by the two-dimensional view and so should never be used without two-dimensional guidance, if at all. End-systolic cavity obliteration is commonly present in cats with severe HCM.

**Systolic anterior motion (SAM) of the mitral valve** - Mitral valve SAM can often be most easily identified using two-dimensional echocardiography, either in real time or in slow motion of a cine loop (see http://www.vmth.ucdavis.edu/cardio/cases/case5/echodopp.htm). Color flow Doppler echocardiography can be used to demonstrate the hemodynamic abnormalities associated with SAM. With this modality one observes two turbulent jets originating from the LVOT - one regurgitating back into the left atrium (mitral regurgitation) and the other projecting into the aorta (dynamic subaortic stenosis). Spectral Doppler is used to determine the pressure gradient across the region of dynamic subaortic stenosis to characterize the severity of the SAM although it can be quite labile, changing with the cat’s level of excitement. Care must be taken not to record the high velocity mitral regurgitation jet. Usually, the dynamic subaortic stenosis jet is narrower (shorter period of systole) than the mitral regurgitation jet; often becoming even more narrow in mid - to late systole.

**Diastolic dysfunction** Diastolic dysfunction in cats with severe HCM has been documented using tissue Doppler imaging (TDI) and measures of transmirtal flow and relaxation time. Cats with severe HCM routinely have a decrease in early diastolic wall motion of the LV free wall and mitral valve annulus using DTI. In addition, on pulsed wave Doppler echocardiography peak E wave velocity may be reduced, peak A wave velocity increased, isovolumic relaxation time prolonged, and rate of deceleration of early inflow reduced in cats with severe HCM when the heart rate is slow enough that E and A wave velocities can be identified.