COMPARISON OF ECHOCARDIOGRAPHY AND COMPUTED TOMOGRAPHY FOR CHARACTERIZATION OF CARDIAC CLOTS IN CATS WITH HEART DISEASE

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THESIS

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ABSTRACT

Arterial thromboembolism (ATE) is a devastating and life-threatening condition in cats most commonly secondary to heart disease. Echocardiography is the reference standard to evaluate for presence of a clot or its precursor known as spontaneous echocardiographic contrast (SEC or "smoke") within the left atrium and left auricle. In humans, trans-esophageal echocardiography (TEE) is the gold standard, however computed tomographic angiography (CTA) is becoming more widely used to assess detection of left atrial thrombi precluding the use of sedation. The purpose of this prospective study is threefold. The first objective is to compare echocardiography and CTA (also dynamic versus continuous phase) in their abilities to identify and characterize cardiac clots from smoke in awake cats. Our second objective is to maximize prognostic indicators and comorbidities (e.g. congestive heart failure, heart chamber enlargement, clots, pulmonary pathology) provided on an emergency basis or when a cardiologist (or echocardiography) is unavailable. Our third objective is to ensure this protocol is safe in cats with heart disease and congestive heart failure. Cats with smoke or clot were recruited and an echocardiogram and CTA (continuous phase and dynamic) were performed within 24 hours. A total of 14 cats were included (7 with clots and 7 with smoke) based on original echocardiographic images. All but one (6/7, 85.7%) of the clots were identified on CTA by at least one reviewer as filling defects within the left auricle (n=6) and right heart (n=1). The highest sensitivity for detection was 71.4% (in continuous phase) and highest specificity was 85.7% (dynamic study). The intra-class correlation coefficient (ICC) showed moderate agreement for both (0.58 for continuous, 0.64 dynamic). Smaller clots, or ones

with incomplete filling of the left auricle, were more likely missed by reviewers on CTA. Echocardiography had low specificity (67%) and poor inter-observer agreement (ICC of .38) with multiple false positives, but had 100% sensitivity – based on original echocardiographic diagnosis. CT provided multiple prognostic indicators and comorbidities: severe diffuse idiopathic pulmonary fibrosis (n=1), asthma (n=1), cardiac enlargement (n=14), left atrial enlargement (n=13), congestive heart failure (5 with pulmonary edema and 8 with pleural effusion), and an aortic thromboembolism. Findings from this study suggest CTA is safe, can identify cardiac clots, provide important prognostic indicators (in patients with heart disease and congestive heart failure), and may be used on an emergency basis or when echocardiography is unavailable.

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CHAPTER 1

INTRODUCTION

Arterial thromboembolism (ATE) is a devastating sequela in feline heart disease and continually an important disease to study due to its high morbidity and mortality rates, acute onset, and common presentation with no history of heart disease.[1] The arterial thrombus most commonly lodges near the aortic bifurcation causing loss of pulses, lower motor neuron signs, cool extremities and extreme pain. These patients are commonly euthanized to prevent further distress, pain and because of the poor prognosis. Cardiac disease is by far the most common origin of these thrombi, more specifically in left atrium and left atrial appendage, secondary to cardiomyopathies.[2] Thrombi form in the left atrium and the let atrial appendage secondary to the dilation, blood stasis, endothelial dysfunction and platelet activation.[1]

Echocardiography has long been the reference standard for the diagnosis and assessment of cardiac disease, including the ability to identify and describe cardiac clots. In cats, poor left atrial appendage contractility and maximum flow velocities (<0.20 m/s) to the left atrium are highly associated with spontaneous echocardiographic contrast (SEC) or ("smoke").[3] Smoke is also a highly accepted marker for a prothrombotic state as well as a predictor of ATE in humans and cats,[4,5] meaning we are able to visualize the precursors of thrombi formation. Contrary to this, at least one paper in humans, has shown thrombi formation with no SEC.[6] Antiplatelet therapy aids in preventing new or further formation of thrombi, and although may prolong life, these patients remain at high risk for ATE.

Humans can suffer aortic thromboembolism or systemic embolism in a similar condition to cats, although cats seem to be more prone than humans or other domestic animals. In humans, approximately 80-90% are cardiac in origin with a high association with atrial fibrillation, cardiomyopathies and less likely myocardial infarction.[5,7] In these patients angiographic radiography or computed tomography is used to evaluate the aortic bifurcation or at the level of patients signs. After a thromboembolism is observed, cardiac assessment via the gold standard trans-esophageal echocardiography (TEE) is performed.

More recently the use of computed tomographic angiography (CTA) is being used in place of echocardiography, as trans-esophageal echocardiography requires heavy sedation and can be painful/mildly invasive.[8] CTA for the detection of clots versus SEC in humans is common now, where a contrast filling defect in the left atrium is consistent with a clot. However in one study they found multiple filling defects (pseudothrombi) in the patients that were in atrial fibrillation and had decreased left atrial appendage emptying. To increase the specificity and positive predictive value to 100% they used a delayed arterial phase at 1 minute.[9] CTA has also shown to have good correlation between other modalities (e.g. MRI, trans-thoracic echocardiography. This included global function parameters, morphology, anatomy and demonstrated good accuracy in humans and small animals – even on the 16-slice CT.[10,11] A newer advancement and additional method for obtaining CT images is using 4D or dynamic (cine-loops), where a specific region of interest is selected dependent on the number detectors of the CT scanner and coverage.[12] The selected region is scanned continually without moving in the Z-direction, the images are reconstructed and viewed in real time, essentially visualizing the heart beating. There have been few studies in animals using 4D and these patients require heavy sedation or general anesthesia. So the

accuracy of assessment of function and clinical relevance needs to be taken into consideration since cardiac patients are poor anesthetic candidates making imaging on an emergency basis difficult.[13]

We relate this to our feline patients, who can have limited or delayed diagnostic imaging due to hemodynamic/cardiopulmonary instability (e.g. dyspnea, CHF, ATE) or no access to a cardiologist (either on an ER basis or within hospital/region). Multiple successful CTA studies, yielding diagnostic images, have been performed in awake healthy and diseased cats.[14,15] The first study used a Plexi-glass positioning device (VetMousetrap™, University of Illinois, Urbana, IL), which precludes the use of anesthesia while providing oxygen, intravenous catheter-based therapy, a low stress environment and ultimately allowing earlier and more complete diagnoses.[15] Another study performed CTA on awake healthy cats using a microdose ($1/10^{th}$) of the normal dose (2.2ml/kg or 660 mgI/kg) of contrast agent and obtained images adequate for evaluating the cardiac chambers.[16]

To the author's knowledge there have been no studies on the comparison of smoke and clots in cats on CT and echocardiography. Our first objective is to compare the ability of CTA to identify and characterize the cardiac clots from smoke in awake cats with echocardiography as our reference standard. We also compare the continuous CT contrast study in previous studies[16] with dynamic acquisition for clot identification. Prognostic indicators for cats with hypertrophic cardiomyopathy have been studied and these include but are not limited to: severe left atrial enlargement, decrease left atrial and ventricular systolic function, extreme left ventricular hypertrophy (>9mm), congestive heart failure,

ATE, gallop, arrhythmia, and regional hypokinesis.[17,18] Our second objective is to maximize the amount of prognostic indicators available to our client and patient, who may have to wait to obtain imaging (e.g. radiographs, echocardiogram). Our third objective is to ensure this protocol is safe and produces diagnostic images in patients with severe cardiac disease and congestive heart failure.

CHAPTER 2

LITERATURE REVIEW

2.1 Heart disease in cats

The term cardiomyopathy encompasses multiple cardiac diseases of the heart in our feline patients and are conditions affecting the muscle (myocardium) of the heart as opposed to the valves such as in mitral valve disease. Cardiomyopathies are by far the most common cardiac disease in cats and hypertrophic cardiomyopathy is the most common subtype. The current list of cardiomyopathies includes hypertrophic, restrictive, dilated, arrhythmogenic right ventricular and unclassified.

Hypertrophic cardiomyopathy (HCM) is characterized by increased cardiac mass and can include hypertrophy of the left ventricle, by way of interventricular septum and/or free wall and may be concentric, segmental, or asymmetric.[19] Approximately two-thirds of people who develop HCM have an autosomal dominant heritable defect (with incomplete penetrance pattern) in one of 11 sarcomeric proteins. Hundreds of mutations in dozes of genes have been discovered in humans with some families expressing novel mutations. Familial HCM has been described in cats, and is caused by mutations in the myosin binding protein C in Maine coon cats and Ragdoll cats.[20,21] Other cat breeds, such as Norwegian forest cats, Persian, Burmese, and Siamese are also suspected of having a primary genetic from of HCM. The etiology of HCM in other cats remains unknown and may be caused by unrecognized mutations. Diastolic dysfunction is the main cause of the secondary cardiac abnormalities such as left atrial enlargement due to the increased filling pressures. The diastolic dysfunction is caused by reduced ventricular relaxation and may be from the

underlying hypertrophy, secondary interstitial fibrosis, loss of myocardial architecture or a combination of all of them.[19]

Restrictive cardiomyopathy is an increase in the stiffness of the myocardium and is the second most common type of cardiomyopathy with two major forms (myocardial and endomyocardial).[19] Like HCM, this type causes restrictive filling of the left ventricle usually resulting in severe left atrial or bi-atrial enlargement. The endomyocardial form can present with extensive secondary fibrotic lesions, even bridging the lumen of the ventricle.[19]

Dilated cardiomyopathy (DCM) is an adult onset primary myocardial disease characterized by dilation of the left ventricular lumen and decreased systolic myocardial function. DCM used to be the most common form of feline myocardial disease until it was determined that many cats suffered from taurine deficiency due to insufficient levels of taurine in commercial pet foods.[22] Grossly there is dilation of the left ventricle, poor contractility, as well as right and/or left atrial enlargement. Now this disease is far less common and may be secondary to another end-stage cardiac disease such as HCM, valvular disease, sustained tachycardia, unrecognized episodes of toxicity, viral infection, or ischemic myocardial disease.[19]

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an adult onset primary myocardial disease characterized by fibrofatty infiltration of the right ventricular myocardium.[23] ARVC is thought of as a right-sided disease with enlargement of the right ventricle, but in some cases the disease included the left ventricle and interventricular septum. The right ventricle can often become markedly enlarged and thin with poor

contractility. These cats may present with arrhythmias, right sided heart failure, and conduction abnormalities.[19]

The last cardiomyopathy is unclassified, meaning that the abnormalities cannot be classified into one of the aforementioned groups. Similar to DCM, this condition may represent an early or end-stage of one of the other conditions.

2.2 Clot development in cat hearts

All of these cardiomyopathies can lead to left atrial enlargement, and as stated above, HCM is the most common cardiac disease in cats and it is common for cats with HCM to develop left atrial enlargement. Left atrial enlargement is the most important risk factor for the development of the left atrial thrombi. But it is not the size alone that creates an environment conducive of thrombi formation, as thrombogenesis is multifactorial. In fact, many cats with enlarged atria do not develop a thrombus further confirming the complexity of this process.

The enlargement of the left atrium and the secondary poor function is known to cause two conditions (endothelial dysfunction and blood stasis) that predispose the left atrium and the left auricle to develop clots.[24] Results regarding hypercoagulability in cats with heart disease have been variable; however, a hypercoagulable environment is present in some cats. These are thought of as interconnected, creating a cumulative risk of thrombus (clot) formation. This principle is known as Virchow's triad, where each of the three arms of the triad contributes to the formation of the clot.

Within the normal heart there is normal turnover of thrombogenesis and thrombolysis, however these three arms of the triad all contribute to clot formation. Adhesion of platelets to subendothelial collagen secondary to endothelial injury is the primary initiating factor for hemostasis.[24] The platelets aggregate at this site while more platelets are activated to allow healing of the endothelial surface. Then secondary hemostasis is initiated whereby circulating plasma coagulation factors contribute to assist in healing of the hemostatic plug. In a normal heart, profibrinolytic mechanisms break down the plug once the endothelium is healed to prevent exuberant clot formation. In cats with an enlarged left atrium and poor auricular function, the ability to empty the left auricle and left atrium is reduced creating blood pooling (or stasis). This decreased ability of the left auricle to rid itself of the precursors to clot formation (or the aggregates of platelets and clotting factors) causes further build up and thrombus formation ensues.

A hypercoagulable state is the third arm of Virchow's triad and may be a local process, from the localized stretching and disease of the atrium, or systemic. Examples of systemic hypercoagulability and thrombus formation include platelet hypersensitivity, decreased antithrombin and protein C activities, and increases in factor VIII and fibrinogen.[24] Identifying hypercoagulability in patients is difficult by using prothrombin time (PT) and activated partial thromboplastin time (aPTT) and has been found to be unreliable and not clinically useful. Newer analyses are becoming more useful to identify hypercoagulable tendencies in cats and include Viscoelastic coagulation monitors (thromboelastography, sonoclot, thromboelastometry).[24,25] Use of these tests in felines has not been implemented as much as in dogs, and may be due to the likelihood of the activation of coagulation factors during sample collection and because they may not

accurately identify hypercoagulable patients as well as hypocoagulable ones because a standard protocol has not been established.[24]

2.3 Feline arterial thromboembolism

The formation of the thrombus (clot) in the heart is critical to evaluate for, identify and prevent, because it is the precursor for feline arterial thromboembolism. However, cardiac disease is not present in every cat with a thrombus. Thromboembolism occurs when a thrombus that is most of the time adhered to the wall of the left auricle, dislodges and enters systemic circulation. The thrombus will inevitably obstruct a vessel and cause infarction or at least partial occlusion of a vessel or arterial bed. The most common site in the cat is the aortic bifurcation (79-85%) and is termed saddle thrombus, feline arterial thromboembolism (FATE) or systemic arterial thromboembolism (SATE)[24]. This is mostly bilateral but can be unilateral. These cats usually present acutely with paresis or paralysis of the pelvic limbs and can have absent segmental reflexes, cold and firm musculature, absent femoral pulses, cyanotic nail beds, and are usually very painful.[24] The theory behind the absent segmental spinal reflexes secondary to the arterial occlusion is an ischemic neuromyopathy from a release of serotonin and possibly thromboxane A_2. These are released from the platelets from induced vasoconstriction of the collateral vessels of the vertebral system and epaxial muscles.[24,26] Also a cause of the extreme pain of these patients may be due to activated platelets that release serotonin which has been shown to stimulate nociceptive sympathetic afferent fibers.[24,27] The clots can go to other vascular beds such as the thoracic limb, which is the second most common site, as well as cerebral, renal and mesenteric

This is a condition that is associated with high mortality and morbidity. Most clinical studies have reported incidences of FATE ranging from 12-28% of cats with heart disease. Specifically, reported percentages of cats that develop ATE with the various cardiomyopathies ranges from: 56% with restrictive cardiomyopathy, 12-17% with hypertrophic cardiomyopathy,[28] 18% with dilated cardiomyopathy.[29] In the general feline population, the reported prevalence has ranged from 1 in 142 to 1 in 175 cats evaluated.[29] The patients are often in distress and the clients (also from personal experience) may be completely unaware of what is occurring to their pet. Most cats presented for FATE have underlying heart disease; however, clinical manifestations are often absent prior to the event. Heart disease may go unnoticed especially in cats for many reasons and the diagnosis of heart disease will be explained in detail later. One of the reasons is the reclusive nature of the cat to hide or an outdoor cat that comes around intermittently and another is that physical exam findings, such as heart murmurs, gallop sounds, and arrhythmias can be absent in cats with underlying cardiac disease. Unfortunately even with acute treatment for FATE, the prognosis is generally poor, owners will commonly elect euthanasia and clinicians will offer this as an option. These reasons show how devastating this disease is and how important detecting and preventing it are. The first 24 hours are also the most distressing and painful and many owners will not want to pursue treatment to prevent any further pain or discomfort to their pet. The short-term prognosis for FATE depends largely on the nature and responsiveness of the underlying heart disease and the owner's willingness to treat. Survival to discharge, in cats with FATE and owners willing to treat, has been reported to be up to 45%.[24] Multiple risk factors have been associated with decreased survival and include hypothermia, reduced heart rate, and absence of motor

function in the affected limbs.[24] The echocardiographic changes that increase the risk of morbidity and mortality will be discussed later. Since treating the primary cardiac condition is not possible with hypertrophic cardiomyopathy and the other cardiomyopathies (excluding taurine-deficiencies), prevention of clot formation is the best option. If the patient/owner elect treatment due to an arterial thromboembolism diagnosis, then immediate supportive care, antithrombotic treatment, and antiplatelet therapy is required. Regardless of decision, pain control should be immediately administered and any patients with concurrent CHF (including pulmonary edema and pleural effusion) should be treated appropriately as well. Surgery is not recommended due high risk of death and thrombus excision is very difficult.[30] Also rapid reperfusion injury after ischemic events can be life threatening. Reperfusion injury is a build up of metabolites including potassium and free oxygen radicals that are released into systemic circulation and can cause arrhythmias, acid-base disturbances, renal dysfunction, and death.[30]

2.4 Treatment of feline arterial thromboembolism

At this time we do not have safe thrombolytic medications or treatments that will lyse the existing clots in cats. As such treatment is geared toward preventing further accumulation of these clots and allowing the body to naturally break them down. There have been multiple attempts to use thrombolytic therapies. One study used tissue plasminogen activator in 11 cats but adverse effects were seen in all cats including azotemia, neurological disorders, arrhythmias, etc. despite seeing signs compatible with thrombolysis in 6/9 cats.[31] Another study used intra-arterial urokinase administration after failure of standard treatments and motor function of both hind limbs with no

complications noted.[32] However this is an invasion procedure, requiring general anesthesia and was only tested in one patient, so further investigation is required. The survival to hospital discharge was not superior to other therapies with thrombolytic treatments.

Since these treatments have not become commonly performed a general consensus for treatment will now be described. Fluid therapy is usually avoided but may be warranted in azotemic patients, although very cautiously. Once pain control, and CHF is either evaluated for, or treated, then antithrombotic therapy and antiplatelet therapy is initiated. Since hypothermia is a risk of morbidity and mortality, keeping the patient in a comfortable, warm environment is recommended as well as passive manipulation and physiotherapy.[30] Decreased pain, increased pulse strength, and motor function are indications that limb circulation is improving. However signs of reperfusion injury and necrosis may occur rapidly so close monitoring within the hospital is recommended. After a couple days of close monitoring these patient with improving signs may be released to their owners to go home – with close monitoring required.

There are two main categories of antithrombotic drugs for cats, similar to humans, and they are antiplatelet agents and anticoagulants. The two most common antiplatelet drugs used in cats are aspirin and clopidogrel (aspirin more commonly than clopidogrel). Aspirin prevents the formation of thromboxane A_2 by irreversibly acetylating platelet cyclooxygenase as well as within the endothelial cells, preventing aggregation of platelets and causes vasodilatory effects.[24] A newer study showed that aspirin was inferior to clopidogrel for secondary prevention of cardiogenic embolism in cats.[33] Clopidogrel is a second-generation theriopyridine that induces irreversible and specific antagonism of the

P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex of the platelet membrane and has more potent inhibitory effect on platelets than aspirin.[24] It also decreases the release of aggregating and vasoconstrictive properties of serotonin and ADP. Clopidogrel was superior to aspirin in a multi-institutional study evaluating the secondary prevention of FATE. Cats receiving clopidogrel had a recurrence rate of cardiogenic embolism of 49% versus 75% for aspirin and 1 year recurrence rate of 36% versus 64% for aspirin. Additionally the median time to recurrence was significantly longer in cats receiving clopidogrel (146 days) compared with aspirin (84 days).[24,34] So clopidogrel is the likely choice going forward in the feline patients that are at risk for developing cardiac clots.

The anticoagulant drugs that may be used are Warfarin and low molecular-weight heparins that work by inhibiting the coagulation cascade and interfering with the coagulation factors preventing clotting (or secondary coagulation). Although not used for primary or secondary prevention in cats, they are the primary choice in humans.[24] Warfarin prevents the formation of vitamin K-dependent coagulation factors II, VII, IX, and X and proteins C and S, which are anticoagulant proteins. Bleeding is the major and minor complication from this medication, it has a variable clinical response and requires routine frequent monitoring, limiting its use.[24] Unfractionated and low molecular-weight heparins prevent the activation of coagulation factor X.[24] These medications have lower bleeding complication rates compared to Warfarin, same as in humans, and may be used more widely than Warfarin. Newer anticoagulants called factor Xa inhibitors in humans are being developed and very little data or use has been done in cats. One medication (rivaoxaban) has shown to have predictable and repeatable anticoagulant effect when administered in

cats and one author thinks that they will have an impact on thrombus prophylaxis over the next 5-10 years.[24] Since our ability to remove or break down these clots is almost nonexistent, our best treatment at this point is prevention. So far my discussion has shown prevention by prophylaxis of the clots, but the diagnosis of heart disease and these clots is an integral part of the treatment and prevention.

2.5 Diagnosing heart disease in cats

In cats the reliability of a murmur to detect heart disease is low, meaning turbulent blood flow can be a benign process in the cat, compared to dogs where usually a murmur is an indication of structural heart disease. In one study of 1007 cats, heart murmurs were present in 40% of apparently healthy cats, and 70% of those murmurs were considered to be functional (no structural heart disease), resulting in a positive predictor value of 17-43% for the presence of a murmur in an apparently healthy cat to detect structural heart disesase.[35] The most common heart disease found in this study was HCM (left ventricular thickness of >6mm) with a prevalence of 14.7%. Essentially this means that many, apparently healthy cats have functional murmurs unrelated to cardiac disease. Also, feline murmurs can be more difficult to auscultate than dogs.

Radiographs using subjective and objective assessments can usually make the diagnosis of heart disease in small animals initially. In cats the specific regions of the heart including the left atrium and main pulmonary artery can be more difficult to assess for enlargement on radiographs so overall size is more important. For cats the cardiac silhouette should be within 2-2.5 intercostal spaces on the lateral projection (or between the fifth rib and the 7th rib. The vertebral heart score should be 7.5 +/- 0.3 on the lateral

view and 3.4 +/- 0.25 on DV/VD image.[36] As mentioned before, overall size should alert clinician of heart disease rather than specific chamber enlargement and unlike dogs, cats could be in heart failure with a normal sized left atrium on radiographs.[37] When left atrial enlargement is seen on the radiographs in a cat, the left atrium is moderately to severely enlarged. However if the left atrium is normal, the patient could still be in heart failure, given that the lung changes are consistent with pulmonary edema.[37] The pulmonary vessels in the same study by Schober et. al. (2014), were not an indicator for heart failure as well. In fact, the pulmonary arteries were more likely to be enlarged than the pulmonary veins, which is inconsistent with canine left heart failure.

Another caveat to feline pulmonary edema is the similarities to other common pulmonary diseases. Consistent with other research, text books, and the author's experience, feline pulmonary edema can appear radiographically similar to other conditions, such as feline lower airway disease (e.g. asthma or chronic bronchitis), atypical pneumonia (e.g. Mycoplasma), and neoplasia (e.g. carcinoma). The classic distribution of feline pulmonary edema is multifocal patchy alveolar or interstitial opacities, or it can display similar characteristics to canine congestive heart failure (CHF). Also feline CHF can be solely or largely pleural effusion. This causes two major drawbacks when evaluating for heart disease or failure in the cat. The first is that pleural effusion can cause border effacement of the cardiac size obscuring assessment of the cardiac silhouette. Pleural effusion differentials for a cat are many but the more common causes are secondary to right or left heart failure, (although right heart failure is much less common than right),[36] pyothorax, chylothorax (which may be associated with heart failure), feline infectious peritonitis (FIP), neoplastic, etc. Secondly, pleural effusion also causes atelectasis of the

lung lobes creating an interstitial to alveolar pattern, which can be difficult to interpret from pulmonary edema. Another characteristic of pulmonary edema is cats is the appearance of bronchial thickening that may be misinterpreted as primary bronchial disease, which is a very common condition in cats. In reality this is peribronchial cuffing (fluid leaking from the vessels into the surrounding interstitium or primary pulmonary disease) mimicking thickening of the walls of the bronchus.[38] So all in all, cat thoracic radiographs can be difficult to interpret, may not always display typical evidence of heart disease, and may be misinterpreted as more benign or malignant disease. This shows how important pursuing echocardiography or advanced imaging can be when a feline patient is displaying signs of congestive heart failure, because the radiographic findings can mimic other diseases and may not exhibit common identifiable signs of congestive heart failure. However, congestive heart failure in cats is very common for cats presenting for respiratory distress, so treating empirically for heart failure as a first line can be life saving.

Radiography may show signs compatible with left heart failure, however specific structural heart disease, function, as well as clots cannot be identified or measured. Echocardiography is the gold standard for evaluating the structure and function of the heart in cats. As explained much earlier there are multiple cardiomyopathies in cats, with hypertrophic cardiomyopathy being the most common. Left atrial and left auricular (auricle) enlargement is the most common sequela and the region of the origination of the clots. On echocardiogram, multiple factors go into a diagnosis of cardiomyopathy and the differences between these will further classify them. A left ventricular wall thickness in diastole of ≥6mm is the most common reference for diagnosis of HCM and that is either focal or diffuse and asymmetric or symmetric in appearance.[36] Other less common

conditions must be ruled that can cause similar left ventricular hypertrophy and these include systemic hypertension, hyperthyroidism, acromegaly, lymphoma, aortic stenosis and muscular dystrophy. Other structural changes that can be seen with HCM are smaller or larger left ventricular volume, hypertrophied papillary muscles, dilated left atrium and left auricle.

The left atrial and auricular dilation, which a very common sequela due to increased atrial pressures is most important for this study as it is the site of clot formation. A newer study showed that reduced fractional shortening of the left atrium was associated with the cat dying from an ATE rather than congestive heart failure.[33] This makes sense because in another paper a left auricular outflow velocity of less than 0.2m/sec indicates the patient is at risk for spontaneous echocardiographic contrast (SEC) which is considered a marker of a prothrombotic state and a precursor to development of clots.[4] This SEC or "smoke" is seen as increased backscatter or echogenicity of the red blood cell aggregates that form due to the low velocity and causes that were discussed earlier. Also, cats with over 0.25m/sec left auricular outflow velocity are considered less at risk of developing a thrombus. Other potential risk factors of a prothrombotic state in that study were the severity of left atrial enlargement, presence of congestive heart failure, and severity of left ventricular diastolic dysfunction. Unlike in humans this study did not find atrial fibrillation as a risk factor for SEC, although all the cats in the study had a low left auricular outflow velocities of under 0.23m/s, indicating poor flow and a high risk for clot formation. When clots form they usually will be confined to the left auricle (commonly adhered to the wall) and appear as an irregular to smoothly marginated echogenic structure of any shape.

2.6 Human thromboembolism and diagnosis

In humans left atrial thrombi occur most commonly secondary to atrial fibrillation and the causes are the same that affect the feline patients (i.e. Virchow's triad) that was previously discussed. However, the main difference between the feline and human causes are that cats almost always have structural heart disease (e.g. cardiomyopathy), as opposed to humans, where the electrical disturbance of atrial fibrillation is the cause in ~60% of all cardioembolic strokes.[39,40] Similar to feline patients, the decreased velocity and function of the left atrium and left auricle secondary to reduced contractility in patients with atrial fibrillation is the cause. Transesophageal echocardiography (TEE) is the gold standard in human medicine to image the left auricle due to its capability to visualize all parts of the appendage and is considered superior to transthoracic ultrasound (TTE) for ruling out left atrial and left auricular thrombi.[39] The thrombi and SEC are similar in appearance to the feline patients and also form within the left auricle more commonly as well. On echocardiography thrombi are typically defined as a well-defined echogenic mass with alternate echotexture than that of the left atrial wall as well as a uniform consistency that is a separate entity from the pectinate muscles of the left auricle.[34] Descriptions of the SEC are usually mild, moderate or severe in echogenicity. Due to the requirements of heavy sedation, and contraindications such as potential esophageal pathology, patients may not be able to have TEE performed and less invasive procedures may be required. In one study, they describe the TEE procedure using topical local anesthetic (Lidocaine) in the hypopharynx with intravenous (IV) benzodiazepine sedation.[6] TEE is also more time consuming than TTE.

More recently contrast enhanced multidetector computed tomography (CE-MDCT) has been proposed as an alternative to evaluating the heart in patients that are not good candidates for TEE. A paper including a responding letter to the editor about said paper discussed the applicability of measuring pre and post contrast Hounsfield units (HU) of the thrombi in assessment of acute and chronic pulmonary thromboembolisms. There is only discussion and no consensus about the accuracy of measuring the thrombi attenuation because there is evidence for acute clots to be isoattenuating on pre-contrast as the contents are very similar to the surrounding blood.[41] This means contrast is required to identify the clots. However, the sensitivity and specificity for identification of the thrombi has a wide range over multiple research papers, until more recently. The wide range of sensitivity, specificity, positive predictor value (PPV) and negative predictor values (NPV), are in large part, due to the poor contractility, flow and mixing of the contrast within the LAA that can result in a pseudothrombus. A high number of patients will be in active atrial fibrillation during the exam, so these pseudothrombi are very common in patients on CT and should not be confused as true thrombi.[42] Left auricular thrombi and pseudothrombi are very similar in appearance on CT, creating a filling defect (or noncontrast enhancing region) within the contrast filled left atrium or left auricle. One paper showed high sensitivity and specificity (100% and 92% respectively) to identify an abnormal left auricle using non-gated CTA while acquiring images of the heart all at once (i.e. using dynamic imaging and using all 64 detectors).[43] They also stated that they were not as accurate to discriminate SEC from thrombus, but a normal CT was very specific for a normal left atrium and left auricle. This paper was later refuted, saying the positive predictor values for identification of true thrombus were so poor that cardiac CT should not replace TEE and

further research should be performed because that means many of the positive CT cases did not have a thrombus.[8] Another study showed that performing a delayed (1 minute) single phase study of the heart again without a second dose of contrast increases the sensitivity, specificity, PPV and NPV all to 100%.[9] The study demonstrated that the filling defect was a pseudothrombus if the left auricle showed homogenous contrast enhancement similar to the remainder of the left atrium on the delayed images. Although, this paper did not cite the other paper mentioned before. In another study they found that quantifying the HU of the left auricle was inaccurate (sensitivity of 85%, specificity of 94%), and that subjective assessment (or visual analysis) was better (sensitivity of 96%, specificity of 100%).[44] But from the author's perspective, this is dependent on dose and image acquisition technique, and may not be useful to compare from one case to another. This is especially true as it applies to feline patients because these human papers now use electrocardiographic (ECG) gating to remove motion and artifact to obtain images with very good spatial and temporal resolution. The same study used a slightly different technique and performed only a scan of the second dose of contrast (or dual enhancement with single delayed phase) at 180 seconds following the first IV contrast dose. The objective was to evaluate for the thrombi only on the second contrast dose since that was the phase that distinguished between thrombi and pseudothrombi on the previous papers. The thought is that there would be more mixing of the contrast within the left auricle and thus higher attenuation values for SEC and lower for the thrombi. A follow up study from the same authors of the previous study, used ECG prospective gating to reduce the radiation doses to the patient and acquire better images. They demonstrated a sensitivity, specificity, PPV, and NPV of 89%, 100%, 100%, 99% respectively for identifying and ruling

in or out LAA thrombi.[44] This sensitivity is lower than the other paper but also described that the HU were significantly different between SEC and thrombus (lower for thrombi than for SEC), which may be beneficial to measure. So there is quite the discrepancy for whether quantitative or subjective analysis is better, but the ability to detect thrombi and differentiate them from circulatory stasis – or patients in atrial fibrillation – is improving. A very recent paper, argues that their high NPV of 95.2% demonstrates that not seeing a thrombus or circulatory stasis basically rules out a thrombus.[39] Also quantitative inspection did not increase any of the parameters to identify nor rule out a thrombus. This means, when a thrombus is not visualized subjectively, measuring the HU's will not aid in predicting a negative result. Most importantly, they claim that in patients with a potential risk that precludes TEE, MDCT using retrospective ECG gating, can replace TEE for ruling out LAA thrombi.[39] However in contrast to other papers, the patients with pseudothrombi and/or atrial fibrillation, the sensitivity (81.5%) and PPV (87.5%) were less accurate than other reports, indicating those patients may require further investigation.

Dynamic CT was briefly mentioned in the previous paragraphs. Dynamic CT is the use of CT in real time, allowing evaluation of changes within attenuation (density) within a specific region over time. A specific slice or region (organ, lesion) is scanned in concert with contrast administration. The changes and characteristics of the region may represent physiologic processes (heart beating) or pathological (portosystemic shunts, tissue perfusion).[45] As described previously, non-gated contrast enhanced dynamic CT has been used to evaluate for cardiac clots in humans but has not become widely used because the inaccuracy of delineating thrombi from SEC. Dynamic ECG-gated contrast enhanced CT has been used in numerous other applications in humans, including but not limited to

pulmonary nodule differentiation of malignant versus benign, cardiac valve and ventricular function, cardiac perfusion.[12,46–51] However the radiation dose is much higher than non-gated and is a concern in humans.[8] In veterinary medicine, this is of less concern to our patients and has been used in multiple scenarios including but not limited to: identifying small pituitary masses, contrast bolus techniques in many diseases, liver nodule and mass differentiation, hepatic perfusion, tracheal collapse, urinary tract conditions (such as glomerular filtration rate, ectopic ureters), pancreas disease (perfusion and mass differentiation).[40,47–52] Dynamic CT is limited by the amount of detectors. For instance our CT scanner is a 16-slice scanner meaning it has 16 detectors aligned on the Z-axis of the patient that can simultaneously and continuously acquire images without moving the patient (or organ). The slice thickness also affects the coverage or length of target organ imaged because choosing a smaller slice thickness will use 16 smaller detectors, thus a smaller coverage and larger slice thickness will use 16 larger detectors, thus larger coverage. So if your target organ (or lesion) is larger than the coverage, than that section will not be scanned. For example, our 16 slice machine will use 1.25mm detectors over 16 slices, so 16 x 1.25mm = 20mm. If we were to obtain thinner slices at 0.625mm over 16 slices (detectors) that would give us coverage of 10mm. In our study we will be looking at the left auricle and part of the left atrium. Although, these appendages are pathologically enlarged in our patients, we hope that this will still suffice, even though identifying if dynamic studies will produce adequate images is part of the study.

2.7 Transesophageal echocardiography in cats

In the feline patients, TTE is the gold standard and TEE is not usually performed due to limited applicability. TEE in feline patients requires general anesthesia and arguably patients should be good anesthesia candidates (i.e. hemodynamically stable). Our feline patients are usually not stable or have structural heart disease and are at risk for anesthetic related death. Secondly, the transesophageal transducers must be pediatric due to the small size of the feline patients and may be cost prohibitive.[58] Furthermore one study showed that the images were not consistently superior to TTE in cats as in dogs or humans.[58,59] So TTE remains the gold standard for evaluating for structural and functional disease and changes of the heart in cats.

2.8 Common presentation in cats and how diagnostic imaging may be delayed

A common presentation for feline patients with heart disease is respiratory compromise or poor cardiac (diastolic or systolic) function. These patients are often given intramuscular (IM) sedation and administered flow-by oxygen or put in an oxygen cage. An intravenous (IV) catheter may be placed to administer medications with quicker onset of action if the patient can tolerate it. During this time a history is obtained and the patient is monitored to better characterize the respiratory pattern and for any improvement. If the patient has a history or pre-existing disease such as heart disease/failure, asthma or chylothorax, the appropriate treatments are likely applied empirically before other diagnostics are performed. These treatments may include thoracocentesis to remove fluid, albuterol for asthmatic cats, or furosemide for CHF. As discussed earlier, feline patients may not have a history of heart disease or this is the first hospital visit. In these cases, the signalment, physical exam (although may likely be minimal), and clinical signs and

characteristics are all used to prioritize the differential diagnoses. If the patient improves or is stable enough to perform diagnostics, thoracic radiographs is usually the first step to provide a global overview and hopefully provide the cause of the clinical signs (i.e. pulmonary and/or pleural space disease) and hopefully insight into the cardiac versus noncardiac disease. If the radiographs are unequivocal for congestive heart failure then treatment (e.g. furosemide) may be adequate until an echocardiogram can be performed. Another common scenario is the radiographs are equivocal and other conditions such as primary pulmonary disease or pleural space disease is complicating an accurate diagnosis.

Commonly these patients present overnight or on the weekend. The presumptive diagnosis of CHF is made via radiographs and they wait until Monday for an echocardiogram, are referred to a cardiologist, or are prescribed medication for presumptive HCM diagnosis. Referring to, or evaluation by, a cardiologist allows confirmation of the presumptive heart disease as cause of the clinical condition, characterizes type and severity of the disease (which includes the prognostic factors), and provides direction of treatment. If an echocardiogram is not pursued or a cardiologist is not available, then the diagnosis is presumed and response to treatment is very important and also guides therapy. In some cases, radiographs and echocardiography are not performed because this requires manual restraint (more so in echocardiography) and the patient is at too high of a risk to be out of oxygen or is easily stressed.

2.9 Prognostic factors in cats with heart disease

As mentioned earlier, but not explained, echocardiography also affords prognostic indicators, for the patient and to the client, that may change the patient's therapy and/or

prognosis. This is also especially important with cases that likely have an aortic ATE. Several prognostic indicators have shown to have a negative effect on survival in cats with cardiomyopathy. In one study of HCM, decreased left atrial and ventricular systolic function, and marked hypertrophy over 9mm, were shown to have increased risk of cardiac death.[60] Increased left atrial size has long been an indicator of poorer prognosis, and a study further confirmed that, as well as showed decreased survival time for the cats in CHF and with an ATE.[60] This study also showed that older age, absence of a murmur, presence of a gallop or arrhythmia, ventricular wall hypokinesis, spontaneous echocontrast, thrombus, absence of left ventricular outflow obstruction, and a restrictive diastolic filling pattern as an increased risk for cardiac death.[18] The cats with syncopal episodes did better than the cats with CHF and ATE, which is different from other and later reports that showed these patients with syncope were more at risk for sudden death than other cats.[33] That same study also showed similar findings that the presence of CHF at presentation and reduced left ventricular fractional shortening, patients were likely to die from CHF within 2 years and asymptomatic cats have a better prognosis.[33] The cats that died from ATE were more likely to have an ATE (or ATE at one point) and decreased left atrial factional shortening. One textbook says that there is a high likelihood of developing congestive heart failure within months to 2 years, when there is significant left atrial dilation.[58] Consistently, the presence of a large dilated left atrium remains a high risk factor for CHF and ATE. Other prognostic indicators in that study included regional wall hypokinesis relating to poor fractional shortening and the presence of a gallop more likely with ATE.[33] Also interestingly in that study, the presence of arrhythmias was not associated with ATE like in humans, but was associated with CHF and sudden death. They also state that the median survival times

ranges for cats are so variable and that rapid progression of structural cardiac changes and poor owner participation, abilities, and insight have worse prognosis. A very recent study showed RCM has a poor prognosis in short and long term compared to HCM (RCM median survival time of 273 days compared to HCM of 865 days).[61] So overall, my take away is that there are many factors that increase the risk of cardiac death and that asymptomatic cats have a better prognosis. Given that the study population or cats that present on an emergency basis are clinical, the asymptomatic aspect is moot.

2.10 Benefits of computed tomography in feline patients

One of the main objectives in the following study is if computed tomography can be a safe alternative to echocardiogram when not available – to be performed over the weekend or in places without a cardiologist – and provide accurate and prognostic value comparable to echocardiogram. We know that CT can provide additional information and there are many causes of thoracic disease. Again remembering that before imaging the diagnosis of heart disease is not yet obtained. Could CT offer benefits that would otherwise be delayed?

Well, as described earlier, in humans CTA has been useful as an alternative to evaluate for some cardiac diseases, most specifically left atrial thrombi. Computed tomography is becoming more and more common in private practice (particularly specialty private practices) in veterinary medicine and also in practices (hospitals) with no in-house cardiologist. There are numerous studies on cats and dogs using general anesthesia and normal contrast injection protocols (1ml/lb. or 2.2ml/kg or 660mgI/kg) to characterize thoracic and airway changes, however our goals are to provide emergency based awake CT

scans in patients that cannot undergo heavy sedation/anesthesia nor full doses of IV contrast. A few CT studies have been performed in cats and dogs that have been stepping-stones to this study and have guided this research. So the following reports will focus on the research on cats that mirrors the current research of this study, meaning awake or non-sedated thoracic CT examinations of cats using the VetMousetrap.™

The first study on awake cats by Oliveira et. al. 2010, used a Plexi-glass restraining device called the VetMousetrap,™ developed by veterinary radiologist Dr. Robert T. O'Brien at the University of Illinois (see Fig. 1). The device is a transparent acrylic tube with a diameter of 21cm, length of 40cm, thickness of 5mm. The idea was to allow the cats to be imaged without direct manipulation as would be required for radiographs and more so for echocardiography. The front of the device has a small slit and hole that allows oxygen tubes to be placed near the patients head as well as catheters to be used for contrast administration or catheter based therapy.

This device was tested in two phases in the study by Oliveira et al 2010. Phase 1 of the study initially tested on normal awake non-sedated cats for changes in ambient temperature, carbon dioxide (CO_2) and oxygen levels. Only one of the ten moved, and the other nine remained quiet and visibly unstressed for the entirety of the exam. The device only had minimal attenuation (~54HU) that did not cause artifacts. The temperature increased over time with the highest at 29°C with no increase in respiratory rate. The inspired oxygen levels increased over time to 95% fraction of inspired oxygen (FiO2) using an oxygen flow rate of 21ml/min and proved to work as an oxygen provider. The end tidal

CO_2 levels increased but to a maximum level of 19mmHg and did not change until over 30 minutes.

Phase 2 of the study by Oliveira et al 2010, tested four different dose-equivalent CT protocols on 22 clinically normal awake non-sedated cats. The four settings were as follows: low and high kV (80 and 120) and two pitches (0.562 and 1.75) that were higher and lower than the normal range, while keeping the dose index volumes the same. To keep the doses the same, manipulation of the mAs was required. The detector configuration was 16x0.625mm creating a beam collimation of 10mm. Reconstructions were made in 1.25mm slice thickness in a detail algorithm. In this phase, supplemental foam wedges were added to assist in keeping the cats in a neutral sternal and similar position to the other cats. This phase also avoided pre scan scout images by keeping the VetMousetrap™ in the same position on the table for each cat and scanning the entire device, producing whole body images. Two cats were excluded due to signs of overt stress. The mean total time for the patient to be at the CT was 12.5 minutes (mostly were below 15 minutes) and the range was 5-28 minutes. After completion of the study they concluded that the protocol with the lower kV provided better contrast, however was not statistically significant. They also showed that motion artifact was minimal, only 5% of the exams had over 10% of the total slices with motion artifact present. Also, even though there was a statistically significant difference between high and low pitches, overall there was absent to minimal motion artifact in a majority of the exams. However there were more helical and windmill artifacts in the protocols with the higher pitch and essentially minimally present to absent in the low pitch protocols.

This study by Oliveira et al 2010, changed the way we can image feline patients by acquiring excellent diagnostic quality images without direct manipulation of awake non-sedated cats. This was in a relatively short period of time in a device that did not alter image quality. Also this device was a presumably low stress environment compared to radiography and echocardiography and provided adequate oxygen therapy and allows catheter-based therapy as well. They suggest a protocol of 80kV, 130mAs, 0.5s rotation time, 0.562 pitch, 1.25mm slice thickness, and 0.625mm slice thickness reconstruction interval with helical based CT examination of the thorax in a cat.[15]

The second follow up study by Oliveira et al 2011, performed CT scans of 54 clinical cats with respiratory disease using the VetMousetrap™ without sedation or anesthesia, with similar protocol in the previous study. These patients had a range of diseases with lung neoplasia (n=9), lower airway disease (n=9), and congestive heart failure secondary to cardiomyopathy (n=9) being the most common three. The severity of clinical signs varied from cough to cyanosis, most of them characterized as dyspneic, and no complications were noted. Oxygen therapy and fluid administration was continued throughout the CT scans. This proved that this protocol and system could be used on cats with respiratory disease and on an emergency basis. However they did have four cats that were unable to have a CT due to instability, so there is some limitation dependent on the patient's clinical status. This study further proved (like many others) that CT is more sensitive for identifying the cause of the clinical signs compared to radiography. For example they reached a correct diagnosis in 77.8% of the cats on CT and 58% on radiography and some of these conditions were lymphadenopathy, feline lower airway disease, bronchiectasis, and cardiomegaly (including congestive heart failure). The CT scan also provided

additional information over radiographs in 74% of the cats and these changes included pulmonary metastases/masses, sternal and cranial mediastinal lymphadenopathy.[14] This was in large part due to CT with contrast performed in 19 of these cats. Although, the study does not mention if the patients with heart failure received IV contrast. So CT not only is more sensitive for identifying abnormalities, it is more accurate for obtaining the correct diagnosis. Furthermore IV contrast can be used in addition to the previously described protocol without complications.

The next study by Rodriguez et al 2014, expanded on the previous studies and looked at using a microdose of IV contrast (0.1ml/lb. or 0.22ml/kg or 66mgI/kg) to evaluate cardiac angiography in normal cats. The contrast dose used was from the author's preliminary data that provided adequate images. These cats were lightly sedated with butorphanol (0.3mg/kg). The purpose was to be able to use these normal parameters for future cases as well as assess visibility of the different cardiac compartments. Meaning the prospective patients would likely, or could have cardiac disease and this may prevent fluid overload, congestive heart failure or further compromise unstable patients. The CT protocol was similar to the two previously described. The contrast was mixed with equal parts saline and delivered via hand injection over 6 seconds. CT attenuation values (HU) and contrast enhancement of the cardiac walls as well as the contrast within the chambers was quantified for normal values. This study also allowed subjective differentiation of the cardiac chambers (specifically all four chambers) using this microdose, and suggest this protocol would be useful for cats with suspected left sided congestive heart failure.[16]

One other unpublished study performed by some of the same author's in the aforementioned reports, looked at cats in congestive heart failure using a similar protocol. In at least one of the CT examinations a contrast filling defect was noted in the left auricle, suspicious of a thrombus (clot), and thus spawned the idea of this project. The next section will outline my research materials and methods to compare echocardiography and computed tomographic angiography for identifying and characterizing cardiac clots in cats with heart disease.

CHAPTER 3

METHODOLOGY

We prospectively recruited cats between 2014 and 2016 with heart disease if they fit the following inclusion criteria on echocardiogram (GE Vivid E9, GE Vingmed Ultrasound, Horton, Norway) performed by our staff cardiologist (RF): (1) spontaneous echocontrast "smoke" and/or (2) a thrombus (clot) within a chamber of the heart. Within 24 hours from the echocardiogram the patient underwent contrast CT of the thorax, or was removed from the study. No specific clinical signs were required. The Institutional Animal Care and Use Committee at the University of Illinois approved our study protocol.

Most of the patients were lightly sedated with butorphanol (doses ranged from 0.2-0.4mg/kg) either intravenously (IV) or intramuscularly (IM) prior to the CT scan and/or echocardiogram. An IV catheter (20-22 gauge) was placed within the cephalic vein. For the echocardiograms, the standard left and right parasternal echocardiographic views were obtained including the oblique left apical parasternal long-axis view, which highlighted the left atrium and left auricle. A diagnosis of cardiac disease along with smoke and/or a thrombus were identified.

A thoracic contrast CT using a 16-slice helical scanner (GE Lightspeed 16 Slice CT, Milwaukee, WI.) was performed with the patient in a Plexi-glass positioning device (VetMousetrap™) in sternal recumbency. Initial scans were pre-contrast routine full thoracic survey series with 1.25mm slice thickness, 0.5s rotation time, small scanned field of view (SFOV), 15cm display field of view (DFOV), 100kVp, 240 mA in detail algorithm. Secondly, a continuous phase (4 runs through heart) post contrast study of the heart (from

cranial to caudal and then caudal to cranial, and so on) was performed using 1.25mm slice thickness, 0.5s rotation time, small SFOV, 15cm DFOV, 100kVp, 320 mA (increased from survey) in standard algorithm and a pitch of 0.9. After approximately a couple minutes, a dynamic (Cine-loop) study was then performed. The protocol used the 16 detectors to obtain 20mm range of image acquisition simultaneously, centered on the region of the left atrium and auricle for 20 seconds. The CT parameters were 1.25mm slice thickness, 0.5s rotation time, small SFOV, 15cm DFOV, 100kVp, 340 mA (increased from survey and continuous phase) in standard algorithm. The region of the left auricle was identified on the pre-contrast study by the radiology resident or faculty (See Fig. 2).

The IV nonionic iodinated contrast medium (Omnipaque 300™ Iohexol injection, GE Healthcare, Princeton, NJ) was delivered by hand injection over 15-20 seconds for both studies (continuous phase and dynamic) and started simultaneously with image acquisition. Hand injections were chosen over power injection because a minimum dose of 10 mls was required for the injector. The IV contrast dose administered was double the microdose used in a previous study[16] to increase the visibility of the margins of the clot and cardiac walls. For example, a patient's dose was 0.2ml/lb. mixed with equal parts sterile saline, which remained a 1/5th of the standard IV contrast dose of 1ml/lb. The same dose was repeated at the beginning of the dynamic (Cine-loop) study. The total IV contrast dose for each patient was 0.4ml/lb., which is below half the standard dose of 1 ml/lb. The total time to set up and run the CT examinations was approximately 5-10 minutes but this is an estimate, as this parameter was not assessed.

All the images (echocardiograms and CT examinations) were anonymized, randomized via a random number generator, and evaluated by two board-certified radiologists (RTO, MH) and cardiologists (RF, JV). The CT and echo images were not compared to each other at the time of review (i.e. the echocardiograms with the dynamic CT studies, or multiphase) to avoid bias. All of the CT images were provided as original (unaltered) DICOM images and manipulation of the window width and level (i.e. switching from soft tissue to lung window) was permitted. The reviewers were given a tutorial on how to open the dynamic images and were allowed to scroll through the detector range (20mm). Only transverse CT images were provided for review, which included: (1) pre-contrast full thorax, (2) continuous phase images over the whole heart and (3) the dynamic (Cine-loop) studies centered over the left atrium and auricle. Only the oblique left apical parasternal long-axis views were evaluated by the reviewers (this included 3-4 short video clips per anonymized patient). However one patient had clots within the right heart, so a right parasternal short axis view of the right ventricular outflow tract was used. The reviewers were given a questionnaire for the echo and CT's to list specific findings (See Table 1). For the CT scan they were asked to answer if the following were present or absent: chamber enlargement (right or left, atrial or ventricular), overall cardiac enlargement, SEC, and thrombi. If present, then they described location and brief description of size. Any additional findings in the CT studies such as pleural effusion or pulmonary disease were evaluated in the same manner and assigned severity (mild, moderate, severe). Artifacts such as motion or contrast streaming were also graded as mild, moderate, or severe, if present and overall CT diagnosis was provided. For the echo's, only

the presence of smoke or clot were asked. If present then location and brief description of severity were described.

On each of the dynamic CTA studies, regions of interest (ROI) were placed within the left atrium, aorta, right atrium and left auricle (at a level of the suspected clot or where the clots typically were visualized within the left auricle). The level, size and position were chosen by the author (KV) but the size and shape of the ROI's were subjectively consistent between all of the patients. The average Hounsfield Units (HU) of these ROI's were collected over the 20 seconds of continuous scanning and put onto a time attenuation curve (TAC). Mean average intensities with 3mm thick slabs were used to acquire more smoothly defined attenuation curves. The raw data was evaluated to assess quantifiably if the mean HU's within left auricles with clots was statistically significantly decreased in contrast enhancement (or attenuation values) compared to the left atrium with smoke.

Statistical analyses for the categorical data were performed with commercially available software.[a] Calculation of sensitivity and specificity for observer's interpretation of post-contrast CT, dynamic (Cine) CT, and echo images for evidence of clot presence was compared to the reference standard of original echocardiographic exam by author (RF). Multiple observers' interpretation was utilized as a mean and rounded to the nearest integer. When observer's answers were indeterminate then these were treated by exclusion from this calculation. Intra-class correlation coefficient (ICC) was calculated for the reliability analysis between the 3 or 4 observers for each modality, echo and CT respectively. Kappa coefficients were also calculated for radiologists and cardiologists for post-contrast and cine CT as well as for the radiologists for the echocardiograms. Statistical

analysis of the continuous data (dynamic cine-loop ROI's) was performed with Microsoft Excel (2010). A 2-sample independent t-test was used to compare between the patients with clots and smoke using the difference of the highest mean attenuation values or Hounsfield Units (HU) of the left auricle and atrium.

[a] IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp.

CHAPTER 4

RESULTS

Fourteen cats were included in the study, diagnosed with either smoke (n=7) and/or clot (n=7) within the heart, based on echocardiography by a cardiologist (RF) as the reference standard. Two of the clots (one of which was highly suspected to be present) at the time of examination were not reproducible in the images given to the reviewers, so the echocardiographic image sets with clots totaled five. The reference number for clots for the CT images remained at seven given the original diagnosis for those two cats included a clot within the left auricles. (See Table 2 to see all the patient info). We did not want to create any bias or false positives for the CT images given that the images likely cover more of the heart (and the left auricle) than echo and may identify the clot if present. All fourteen cats had the same echocardiographic and CT protocols. The only other difference was a patient with a suspected FATE that had an additional microdose to confirm a (filling defect) thrombus within the aortic trifurcation during an abdominal study. No complications were noted with any patients using this protocol, although specific parameters were not assessed.

Six out of the seven (85.7%) clots were visible on CTA as filling defects by at least one reviewer using the continuous phase and 5/7 (71.4%) clots in the dynamic (CINE) studies (See Table 3). For one the clots that was missed in the dynamic phase, at least one observer had an indeterminate response (meaning unsure or possibly present). The sensitivity and specificity for detection of a clot on continuous phase was 71.4% for both.

The intra-class correlation coefficient (ICC) was 0.58 (moderate agreement) and the kappa values were 0.26 (fair agreement) for the radiologists and 0.45 (moderate agreement) for the cardiologists. For the dynamic studies, the sensitivity and specificity were 57.1% and 85.7%, respectively. The ICC was 0.64 (moderate agreement) between all reviewers and the kappa values were .36 (fair agreement) for the radiologists and .47 (moderate agreement) for the cardiologists. (See Table 4). No clots (filling defects) were visible on pre contrast images.

Three clots were confirmed on necropsy within the dilated right heart of one patient with severe cardiomyopathy, cardiac fibrosis, chronic infarctions, and os cordis (skeletal bone within the heart). Two other patients had necropsies, one was a smoke patient confirmed to have no clots. The other patient had a presumed (highly suspected) left auricular clot (on echocardiography and CTA) and FATE. The necropsy showed no left auricular clot but did confirm large thromboembolism within the aortic trifurcation. The locations of the clots on CTA within the chambers of the heart corresponded to the echocardiographic location in all cases (one within the left auricle of six patients and three within the right heart of one patient). Most (5/7) of the left auricular clots on transverse CTA exam appeared as fairly well defined, irregularly marginated, mildly variably sized non-contrast enhancing filling defects occupying the left auricle from its distal aspect. The border of the clots that occupied the left auricles adjacent to the contrast was always mildly concave (see Fig. 3 which compares clot and smoke images). Six of these clots were within the distal aspect of the left auricle and the three right heart clots randomly bordered the endocardial surface of the right ventricle and right ventricular outflow tract (see Fig. 4). The shape of the clots mildly varied between CTA compared to echocardiogram. On

echocardiography they were irregularly marginated and mostly incompletely filled the left auricle with surrounding or intermixed regions of anechoic blood or echogenic smoke. However, on the CTA exams these commonly homogenously filled the left auricle. The two patients with a small thrombus and suspected thrombus (within the original echocardiographic diagnosis but only smoke on echo images given to the reviewers) displayed a small filling defect similar to the appearance of the other small thrombi and were detected by at least one of the reviewers in both cases. This likely indicated that the CT was able to identify that clot rather than a false positive, since the original examination either had a clot (n=1) or highly suspected a clot (n=1).

The echocardiographic sensitivity to identify a clot was 100% but the specificity was 67%. The ICC for all three observers was 0.38 (poor agreement) and the kappa statistic for the radiologists was 0.39 (fair agreement). All of the clots (5/5) were visualized by all of the reviewers (i.e. no reviewer missed a clot) but all of the examiners had at least one false positive (both the radiologists had multiple false positives).

Diagnoses in these cats with cardiac disease were all cardiomyopathies, including hypertrophic (n=9), unclassified (n=4) and restrictive (n=1). Final diagnoses for the heart diseases were based off of echocardiography (n=11) and necropsy (n=3). Other findings included one patient with severe diffusely thickened and hyperattenuating interlobular septa throughout the lung parenchyma on noncontrast CT, consistent with diffuse severe idiopathic pulmonary fibrosis (see Fig. 5). One cat had poorly defined soft tissue attenuating thickening of the bronchial walls, and asthma was presumed. Eight patients had signs consistent with congestive heart failure diagnosed via echocardiography and concurrent radiographs (5 with pulmonary edema and 8 with pleural effusion). All of these

patients were diagnosed with cardiac disease and failure on the pre contrast images. The pericardial fat even allowed accurate identification of left atrial and auricular enlargement between all the viewers to make the diagnosis before contrast was administered. The pulmonary edema commonly manifested as mild ill-defined patchy interstitial pattern (ground glass appearance) to marked patchy ill defined increased attenuation with border effacement of the surrounding vessels and air bronchograms (alveolar pattern) within multiple lung lobes (see Fig. 6). The location was variable and was sometimes more peripheral. Some of the marked alveolar patterns appeared mass-like in the lung window, however on the soft tissue window was non-contrast enhancing. In all of the pulmonary edema cases there was ill-defined perivascular soft tissue attenuation causing border effacement of the vessels and at least mild venous congestion was present in all the cases with congestive heart failure. Minimal pericardial effusion was present within 9 cats (diagnosed by echocardiography) but none were identified on CTA. A contrast filling defect was identified on CTA in one patient and a corresponding thrombus was confirmed at the aortic trifurcation on necropsy. On CT the filling defect extended into the terminal aorta, and external and internal iliac arteries (See Fig. 7).

The age ranges of the patients were from 1-17 years old (median age of 10). There were 9 male castrated and 5 female spayed cats. The most common breed was domestic shorthair (n=9), then Sphynx (n=3), domestic medium hair (n=2), and one mixed breed. The presenting complaints of the cats mildly varied with the most common being an increased respiratory rate and effort (n=8). Three presented for difficulty walking or possible saddle thrombus and one was a recheck heart disease that was nonclinical at the time of exam. The clinical signs ranged from one doing well to open mouth breathing. Most

of them had increased respiratory effort and rate (n=7) and two had open mouth breathing and dyspnea. The two cats with open mouth breathing were imaged after they were stabilized and respiratory character improved. Three cats were neurologically inappropriate with ataxia and paresis or -plegia; one had central vestibular signs. These patients were suspected to have arterial thromboembolism causing these clinical signs.

The ROI's obtained from the dynamic studies were compared between the clot (n=7) and smoke patients (n=6). One of the patients file was corrupted and the values were not obtainable. Another patient, the exam only recorded half of the data. The null hypothesis is that the group's (clot vs. smoke) differences of highest attenuation values (HU) would be the same (or statistically not different). A confidence interval of 0.95 and p=0.05 was used to assess statistical significance between the two categories. The one tailed t-value was 1.8125 and the P-value was 0.0209. The null hypothesis was rejected, indicating a statistical difference between the clot and smoke groups. The clot group had significantly larger HU difference between the left auricle and left atrium compared to the groups with smoke. Specifically the left auricle had lower attenuation values compared to the left atrium.

CHAPTER 5

DISCUSSION

All but one of the clots (6/7) identified on echocardiography were identified as contrast filling defects on the post contrast CT studies by at least one of the reviewers. The highest sensitivity for detection was 71.4% in the continuous phase post contrast studies. The only clot that was not detected by any of the reviewers was smaller, incompletely filled the left auricle, and had contrast surrounding the clot within most of the left auricle – unlike the other five clots. This likely indicates that identification of the clot is viewer and location dependent. Meaning that a smaller clot, one that incompletely fills the left auricle, or is more mobile with surrounding contrast, may be missed. Identification is also likely dependent on a viewer's experience, not necessarily on years of experience, but more so one that has seen more of these cases and has given more attention to the normal left auricular appearance on CTA. The poor to moderate inter-observer agreement using the ICC and kappa statistics further confirm this. Giving the reviewers a normal left atrial study or examples of CTA images with and without a clot likely would have increased the sensitivity, specificity and inter-observer agreement, since this is a novel region of interest in the heart to evaluate. The movement of the filling defects within a single study (i.e. the left auricle moving in and out of the image plane) may have contributed to some reviewers missing some of the clots because they assessed for a persistent filling defect. Also within the dynamic studies the reviewers were asked to toggle through the 2cm of slices at 10 images/sec, which could also decrease the sensitivity. The highest specificity was 85.7% on the dynamic studies (not too dissimilar from the continuous phase at 71.4%). The pectinate

muscles within the left auricle pose a problem as they cause undulating filling defects extending from the wall that may be confused as clots and likely contributed to some of the false positive diagnoses in these cats. Another factor is the movement of the heart during the exam, which causes motion artifact and partial averaging of the wall, which also likely contributed to the false positives. Nonetheless, this does not negate that all but one of the clots identified on echo were visible as contrast filling defects in the CTA studies. Furthermore, the one that was missed is visible on both the continuous phase and dynamic studies by the lead author. Again this was likely missed by the reviewers due to the unfamiliarity of assessing this appendage and dissimilarity of the clot from the others. The more well defined clots, ones that homogenously filled the left auricle, as well as the larger ones were seen by all of the reviewers and consistently. The authors believe that the more cardiac disease is studied (such as this research) and used with CTA, the sensitivity, specificity and observer agreement for identifying cardiac clots will increase.

The continuous phase studies were more sensitive than the dynamic studies (71.4% compared to 57.1%), likely because all of the reviewers were unfamiliar with or had not used the 4-D tools to evaluate the heart in real time. Allowing them to toggle through the image planes while playing the loops in real time likely hindered their ability to detect the clots. The dynamic study was limited to 2cm (due to our 16 detector limit) and in almost every image the entire left atrium and auricle could not completely be within this coverage (e.g. image set). The author centered on the tip of the left auricle and the CT scanned 1cm cranial and caudal to this location. The images also contained more motion artifact and partial averaging, all of which likely contributed to poor detection and increased indeterminate responses. So as these CT dynamic studies become more user friendly and

commonly applied, this will likely increase the detection accuracy. The continuous phase studies had less motion artifact, with subjectively better spatial resolution.

Another interesting finding was the low specificity (67%) for reviewers to rule out clots echocardiographically compared to CTA (lowest was 71.4%). The reviewers commonly had false positives (and more common with the radiologists). The results from this study and feedback from the reviewers show that identification and differentiation from smoke on echo can be challenging in some cases, especially with a severe amount of smoke. To say that CTA is more specific than echo would be difficult to extrapolate and further investigation and research is needed. Only having the selected echo clips and the nature of retrospectively viewing another cardiologist's images is a limitation of this study. One benefit of CTA may be the ability to evaluate the entire left atrium and auricle, which can be difficult echocardiographically, especially in cases with severe left atrial and auricular enlargement. In contrast, the sensitivity was high (100%) and none of the reviewers missed a clot. This is not surprising given that echocardiography is the reference standard for diagnosing clots but also reassuring, as it was the reference standard for this study. Some of the clots characterized on echo were mildly different in size and shape (mostly smaller on echo) compared to the CTA but were all localized accurately within the heart by CTA (n=6 in the left auricle, n=1 each in the right atrium, RVOT and right ventricle). The authors believe this mild size and shape discrepancy is likely due to pooling of blood (stasis) around the clot because of the poor cardiac contractility and ability to eject blood out of the left auricle from around the clot. To the author's knowledge, there is no distinguishing characteristic of smoke on CT so this was not assessed on the CT images. Also, severe smoke or stasis within the left auricles without clot formation but with a filling

defect on CTA is possible given that the stasis surrounding the clot increases the size of the filling defect. Further research in patients with severe smoke and concomitant conditions like atrial fibrillation compared to the Hounsfield Units may be useful.

We found that CT was able to provide some valuable prognostic indicators and comorbidities, even though the amount of cardiac information provided by CT scans (such as function) does not compare to echocardiography. Although prognostic factors such as fractional shortening, regional wall hypokinesis, and left ventricular function cannot be evaluated, CT provided multiple prognostic indicators in most of the patients including: atrial or ventricular clots (6/7), severe left atrial enlargement (n=13), cardiomegaly (n=14), congestive heart failure (n=5 pulmonary edema, n=8 pleural effusion) and confirmed a thromboembolism in the aortic trifurcation (n=1). These findings were very consistent among the reviewers so statistics was not performed.

There is very little literature on the CT appearance of pulmonary edema in cats, likely because these patients are usually screened before CT exam for heart disease and patients at most institutions and hospitals are under general anesthesia, precluding CT exams. The CT findings of pulmonary edema in these cats were similar to the previously reported variable radiographic appearance and shared commonalities described in the results.[62] This study confirms and adds to the literature of CT appearance of pulmonary edema in cats. The CT's also provided additional comorbidities including severe diffuse pulmonary fibrosis, presumed asthma and arterial thromboembolism. The distribution of the cat with presumed idiopathic pulmonary fibrosis was similar to a previous report and literature, showing diffusely thickened and hyperattenuating interlobular septa.[45,53,63] All of

the reviewers accurately identified overall cardiac and specific chamber enlargement on both pre and post contrast CT images, although all the cats had heart disease. Specific sizes of changes (e.g. left atrium, interventricular septum) and type of cardiac disease (e.g. hypertrophic cardiomyopathy) were not evaluated in this study. A good future study would be to compare measurements such as left atrial to aortic (LA:AO) ratio on CTA to echocardiography in patients with cardiac disease in this type of setting (i.e. without general anesthesia).

CT failed to identify all cases (n=9) with pericardial effusion even though the amount was termed trivial by the cardiologist. Previous reports and text consider that CT may be accurate in identifying pericardial effusion however only a small amount of pericardial effusion over 50mls in a human study was detectable. Furthermore the veterinary literature is in dogs which all arguably were larger patients and had a larger amount of effusion.[53,64,65] These cats only had a very minimal amount, many had bordering pleural effusion, and the wall of the pericardium is only 1-2mm thick in normal cats.[53] Also there is likely motion artifact and partial volume averaging given the cats are awake and non-gated CT was used. So the poor sensitivity of the CT scan to detect trivial pericardial effusion is not surprising.

The dynamic studies showed there is a statistical difference of the left atrial and auricular mean HU's between clots and smoke. This is further proof that the filling defects within the left auricles (and right heart) are true. However, previous research in humans has shown that quantifying the left auricle attenuation values is less sensitive and specific compared to subjective visual identification.[39] The clinical applicability of measuring the

HU's within these regions is likely low. This is especially true given that a low specific (threshold) number was not reached to accurately assess if a clot was present and running a TAC for clinical cases would be time consuming. Also, the left auricle seems to have consistent lower attenuation values than left atrium normally (or in cases without a clot) (See Fig. 8). This protocol was standardized as much as possible by the author, but placement and size of the ROI's is user dependent and subjective. Further standardization of the placement and size is likely needed but this study can be used a starting point. Future studies using this technique with more cases are needed. Also, using a larger row of detectors may provide more useful information for this type of study and other conditions in addition to cardiac disease.

The study protocol using the doubled microdose over 15-20 seconds proved safe to use in awake cats with severe heart disease and congestive heart failure. The author does not propose that this protocol would be innocuous in all cats with severe cardiac or respiratory disease – the decision would be patient and clinician dependent. As such, the two cats with severe dyspnea in this study were stabilized before the exams. Nevertheless most of the cats were symptomatic during the exam with no visible or overt cardiovascular changes noted post examination. This study adds to the literature that CTA can be useful and safe in a patient with cardiac disease and failure that may have diagnostic imaging delayed due to instability or no access to a cardiologist. The intent of this study was never to replace echocardiography. In fact, many times the patient's clinical signs may be equivocal and CTA can now be used in these cases. Cardiac disease can present similar to many other thoracic diseases and the diagnosis of heart disease is not made until imaging is performed. Since the cardiac size and diagnosis on the pre contrast images were very

accurate for heart disease and failure, this protocol can be substituted in for the patients that require contrast. A future study would be to use this protocol for patients presenting with primary extra-cardiac disease (such as pulmonary neoplasia) and concomitant cardiac disease precluding the use of a normal contrast dose – to evaluate if the microdose will provide enough contrast to discern neoplasia from other diseases.

Only mild artifacts were found in this study, mostly pertaining to streaking artifact within the right atrium due to contrast mixing and motion artifact. Neither of them hindered interpretation of the images and were all deemed good diagnostic studies by the reviewers, similar to previous studies.[14–16]

There are some additional limitations in this study. The echo images only provided three to four clips of a specific region of the heart (chosen by one of the authors) and were not representative of the full study or of the left atrium and left auricle. This is why there was a discrepancy of the number of clots in the echo and CT images. This also makes the ability of determining the sensitivity and specificity a little more difficult and convoluted, because the presence of the clot is dependent on the original echocardiographic exam. Also, post mortem exams were only performed on a few of the cases to confirm the presence of the clots and in one case with a left auricular clot on echo, no clot was found on necropsy. The patient also had an arterial thromboembolism, so the left auricular clot could have dislodged by the time of the necropsy. Other possibilities are that specific attention to the heart was not specified on the post mortem request or the echo and CT identified a false positive. The CT images were only reviewed in original transverse planes and the ability to make multiplanar reconstructions may have improved detection. Only a small number of

cats (n=14) and only with heart disease (abnormal cats) were used in the study. Comparing these images to normal may have given the reviewers better accuracy and reference to left auricular anatomy, such as pectinate muscle appearance. Normal cats are the standard control group for most studies and may have allowed a better control for this study. However assessing for cardiac clots in normal hearts would likely not be performed in a clinical basis.

CHAPTER 6

CONCLUSION

In conclusion, CTA can be a safe and informative diagnostic imaging modality in awake cats with severe cardiac disease and congestive heart failure using our altered microdose protocol and VetMousetrap.™ CTA can detect cardiac chamber enlargement and clots, although smaller clots or ones incompletely filling the left auricle may be missed. Both dynamic and continuous image acquisition can be useful, but continuous phase may currently be more sensitive. CTA also provided important prognostic indicators including congestive heart failure (pulmonary edema, pleural effusion), severe left atrial dilation, cardiac clots and arterial thromboembolism.

CHAPTER 7

FIGURES AND TABLES

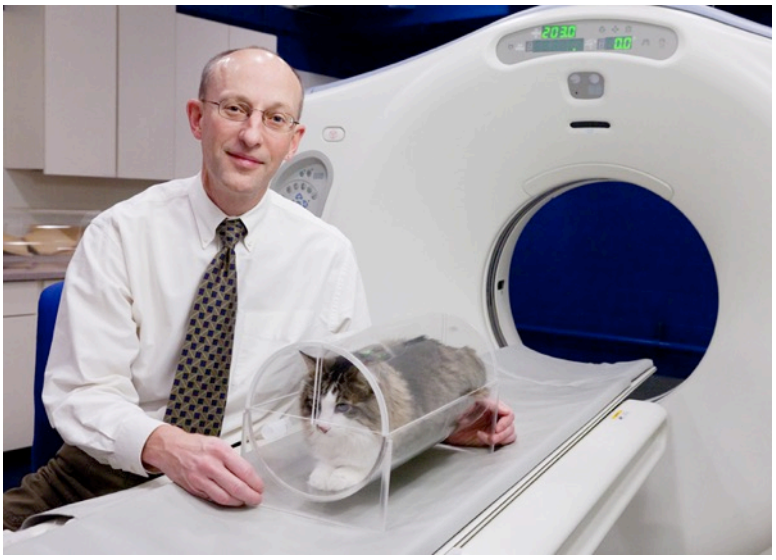


Fig. 1. Dr. Robert O'Brien and a feline patient within the VetMouseTrap™ he developed on the CT scanner table. (https://news.illinois.edu/blog/view/6367/204877#image-1)



Fig. 2. Pre contrast transverse CT at the level of the left auricle (white arrow) in a soft tissue window. Patient's right is on the left. Soft tissue window (WL: 40, WW: 350).

Patient ID	Smoke (yes or no, indeterminate)	If Smoke: mild, moderate, severe; descriptor (LMNOSS)	Clot (yes or no, indeterminate); descriptor (LMNOSS)
A			
B			
C			
D			
E			
F			
G			
H			
I			
J			
K			
L			
M			
N			

Name of Evaluator:

Table. 1. (cont.)

Image set #	Filling defect - Clot (yes or no, indeterminate); Description (LMNOSS)	Subjective cardiac/chamber enlargement (mild, moderate, severe)	Additional findings (e.g. pleural fuid, pulmonary edema, vessel changes, pulmonary nodules, lymph nodes, pericardial fluid)	Artifacts (e.g. motion, streaking) and severity (mild, moderate, severe)	Diagnoses
Cat 1					
Cat 2					
Cat 3					
Cat 4					
Cat 5					
Cat 6					
Cat 7					
Cat 8					
Cat 9					
Cat 10					
Cat 11					
Cat 12					
Cat 13					
Cat 14					
Cat 15					
Cat 16					
Cat 17					
Cat 18					
Cat 19					
Cat 20					
Cat 21					
Cat 22					
Cat 23					
Cat 24					
Cat 25					
Cat 26					
Cat 27					
Cat 28					
Cat 29					
Cat 30					
Cat 31					
Cat 32					
Cat 33					
Cat 34					
Cat 35					
Cat 36					
Cat 37					
Cat 38					
Cat 39					
Cat 40					
Cat 41					
Cat 42					

Table 1. (cont.) Questionnaire's given to the reviewers for echocardiography and CTA, respectively.

Patient #	Age	body weight (kgs)	F/M (I/N)	Breeds	Presenting complaint	Clinical signs	Physical exam	Diganosis	Necrospy?
1	11	6.13	MC	DSH	increased breathing effort	3- hx of inc resp effort, hx of presumed asthma	III/VI left parasternal sys murmur, harsh diffuse lung sounds, expiratory click	HOCM (**smoke** by echo), pulmonary fibrosis, mild pericardial effusion, CKD, HyperT4, IBD/GI lymphoma, suspect UAI with bact pneumonia	No
2	9.5	3.8	MC	DMH	respiratory distress	few day hidstory of breathing heavy	arrhthmias	Unclassified cardiomyopathy (right atrium enlarged, mild pulmonary hypertension, severe **SEC**, trivial pericardial) and pulmonary edema, mild pleural effusion, frequent VPCs, possible FIP	No
3	3	8	MC	DSH	possible saddle thrombus	dragging hindlimbs	IV/VI left parasternal sys murmur, absent femoral pulses bilaterally, crackles in all lung fields, inreased effort, no motor, withdrawal, or nociception in hind limbs, cool extremities	FATE, CHF, HCM, pulmonary edema, Small left auricular left Au **clot**, mod mit regurg, severe left atrial enlargement, mild pericardial and pleural effusion.	Yes, aortic trifurcation, no gross cardiac abnormalities (no clot).
4*	10	2.9	FS	DSH	difficult walking/ abnorml heart rate	decreased mentation, left slight head tilt, mild ataxia,	tachypnea, arrythmia, decreased mentation, left slight head tilt, mild ataxia, mild mit regur, smoke and small thrombus in le Au, right atrium mod enlarged, minimal pericardial effusion.A fib,	HCM with suspect FATE, mild mit regur, smoke and **small thrombu**s in le Au, right atrium mod enlarged, minimal pericardial effusion.A fib, likely asthma	Alive
5	1	3.77	FS	DSH	Respiratory distress	tachypnea	crackles noted in all lungs, increased effort and rate,	Left atrium severely enlarged, **SEC** in le At and Au, HCM (compensated)	Alive
6*	17	3.1	MC	DSH	Respiratory distress and inappetance	seizure like episodes, ataxia, vestibular events, PU/PD, low activity, losing weight	depressed, tachypnea, mydriatic pupils, gallop rhythm, increased respiratory effort, shallow breathing, PLR's decreased	Restrictive cardiomyopathy possible end stage HCM, **suspect or possible Lau thrombus (but only see SMOKE)**, Ventricular arrhythmia (single rare PVCs and APCs), right heart dilation, decreased function, mod to sev tric regurg, scant pericaridal and trivial pleural effusion (CHF).	No
7	6	4.23	MC	DSH	Respiratory distress	inreased respiratory effort, severe dyspnea, pale MM, hypothermia,	increased effort and respiratory rate, severe arrythmia, lung sounds decreased	Myocardial fibrosis suspect restrictive cardiomyopathy, systolic dysfunction chronic myocardial infarction, **SMOKE**, moderate pleural and trivial pericardial effusion, chronic chylous pleural effusion	No
8	10	4.6	FS	Sphynx	lethargy and anorexia, respiratory distress, pleural effusion	increased effort and rate,lethargy and anorexia	cyanotic MM, CRT >2secs, decreased lung sounds, increased effort and rate	Right ventricular masses (or **thrombus**), right ventricular dilation and right and left systolic dysfunction possilbe myocardial infarction, left myocardial infarction, pericardial pleural effusion (CHF),	Yes, three thrombi, Cardiomyopathy, with presumptive intraventricular thrombi and left ventricular dilation, pleural effusion (l-CHF), asciate (R-CHF), fracture quadrate liver lobe, congestion, mild hemorrhage, Pulmonary edema, cardiac fibrosis from chronic infarctions, os cordis (skeletal bone in heart)

Table 2. (cont.)Patient data.

9	8	5.31	FS	DSH	progressive hindlimb paralysis over 24 hours	acute onset hindlimb lameness, unable to use back legs, knuckled sometimes,	bradycardic, intermittent VPCs, left wheezy lungs, NA parapaesis, poor pulses in hindlimbs	HCM, La smoke and **CLOT**, Ventricular arrythmia, trivial pericardial effusion, pulmonary edema, suspected FATE	Alive
10	11	3.9	MC	Mixed breed	recheck for HCM	doing well	gallop rhythm	HCM (stable) with La smoke and **CLOT**, CKD, IBD, very mild pleural effusion (cylous effusion),	No
11	9.5	2.35	MC	Sphynx	anorexia and lethargy, febrile	anorexia, lethargy, febrile,	febrile, tachypnea,	G III/VI left murmur, arrythmia, HCM with **smoke** improved CHF (pulmonary edema and pleural effusion, PVCs,	No but later developed presumably FATEs
12	12	4.3	MC	Sphynx	respiratory distress	3 week hx of difficultly breathing, heart murmur,	gallop, murmur, pulse deficits, jugular distension, arrythmia, tachypnea, hypertension, VPCs, ventricular bigeminy, muffled heart, increased resp effort	improved CHF (pleural effusion and pulmonary edema), Unclassified - systolic dysfunction, biatrial enlargement, R and L CHF, pericaridal and pleural effusion, **SMOKE,** peritoneal fluid, CKD,	Alive, developed La thrombus, atrial fibrillation
13	10	3.18	MC	DMH	open mouht breathing, pleural effusion and pulmonary edema	open mouth breathing	mydriatic pupils, gallop rhythm, III/VI left para murmur, slightly shallow resp in creased effort	HCM, Myocardial fibrosis (Chronic infarct),trivial pericardial effusion, SEC and small **CLOT**, metastatic madibular Carcinoma LN met from?	NO, but likely Carninoma mets to lungs and euthanized, Hyperthyroidism
14	12	3.65	FS	DSH	gallop rhythm and HOCM	gallop rhythm,intermitt ent increased resp rate	tachycardia, IV/VI left para murmur,	HOCM, PVCs, **SEC**	YES: present for suspected saddle thrombus, Histo: myocardial fibrosis, pulmonary edema, NO CLOT noted.

*=On original echo or highly suspected, but not on echo key

Table 2. (cont.) Patient data.

CT Key

Annon Name	Annon ID	Clot (0=no, 1=yes) CT Key	Clot (1=yes, 0=no, 2, indeterminate) Observer 1	Observer 2	Observer 3	Observer 4
Pre Full Cat 29	29	0	0	2	0	2
Pre Full Cat 34	34	0	0	2	0	2
Pre Full Cat 26	26	0	0	2	0	2
Pre Full Cat 16	16	1	0	2	0	2
Pre Full Cat 32	32	1	0	2	0	2
Pre Full Cat 39	39	0	0	2	0	2
Pre Full Cat 21	21	1	0	0	0	2
Pre Full Cat 15	15	1	0	0	0	2
Pre Full Cat 36	36	0	0	2	0	0
Pre Full Cat 17	17	0	0	2	0	0
Pre Full Cat 28	28	1	0	2	0	2
Pre Full Cat 10	10	1	0	2	0	2
Pre Full Cat 40	40	0	0	2	0	2
Pre Full Cat 9	9	1	0	0	0	0
Post Full Cat 27	27	0	0	0	0	0
Post Full Cat 23	23	0	1	0	0	0
Post Full Cat 31	31	0	1	2	0	0
Post Full Cat 5	5	1	1	1	1	1
Post Full Cat 37	37	1	1	1	0	0
Post Full Cat 11	11	0	1	2	1	2
Post Full Cat 1*	1	1	1	0	0	0
Post Full Cat 25	25	1	0	2	0	0
Post Full Cat 24	24	0	0	2	0	0
Post Full Cat 7	7	0	1	0	0	0
Post Full Cat 22*	22	1	1	1	1	1
Post Full Cat 41	41	1	1	0	0	1
Post Full Cat 12	12	0	1	1	1	1
Post Full Cat 2	2	1	1	1	1	1
Cine Cat 14	14	0	0	0	0	0
Cine Cat 38	38	0	1	0	0	0
Cine Cat 33	33	0	1	2	0	0
Cine Cat 20	20	1	1	1	0	1
Cine Cat 4	4	1	1	1	1	1
Cine Cat 30	30	0	1	2	0	0
Cine Cat 19*	19	1	1	0	0	0
Cine Cat 8	8	1	0	0	0	0
Cine Cat 13	13	0	0	0	0	0
Cine Cat 3	3	0	0	2	0	0
Cine Cat 35*	35	1	1	2	1	1
Cine Cat 6	6	1	0	2	0	0
Cine Cat 18	18	0	1	1	1	1
Cine Cat 42	42	1	1	1	1	1

*= clot on original echo or highly suspected, but not in echo to reviewers

Echo key

Patient Folder	Clot (1=yes, 0=no)	Observer 1	Observer 2	Oberver 3
A	1	1	1	1
B	0	1	2	1
C	0	0	2	0
D	0	0	2	1
E	0	1	0	0
F	1	1	1	1
G	0	1	0	0
H	1	1	1	1
I	0	1	2	1
J	0	0	0	0
K	0	1	0	0
L	1	1	1	1
M	0	0	2	0
N	1	1	2	1

Table 3. Results from reviewers for clot detection on CTA and echocardiography.

Post Contrast CT						
ICC all 4 observers	0.58	95% CI: 0.053 to 0.84	p=0.018	Moderate reliability		
Kappa 2 radiologists	0.26					
Kappa 2 cardiologists	0.45					
Observers		**CT post Key**				
	No	Yes				
No	5	2	7		Sensitivity	0.714285714
Yes	2	5	7		Specificity	0.714285714
	7	7	14			
Cine CT						
ICC all 4 observers	0.64	95% CI: 0.18 to 0.87	p=0.007	Moderate reliability		
Kappa 2 radiologists	0.36					
Kappa 2 cardiologists	0.47					
Observers		**CT post Key**				
	No	Yes				
No	6	3	9		Sensitivity	0.571428571
Yes	1	4	5		Specificity	0.857142857
	7	7	14			

Table 4. (cont.).

Echo						
ICC all 4 observers	0.38	95% CI: -0.52 to 0.78	p=0.14	Poor reliability		
Kappa 2 radiologists	0.39					
Observers		**Echo Key**				
	No	Yes				
No	6	0	6		Sensitivity	1
Yes	3	5	8		Specificity	0.666666667
	9	5	14			

Table 4. (cont.). Inter-observer agreement, sensitivity and specificities for echo and CT studies (including continuous phase and dynamic).

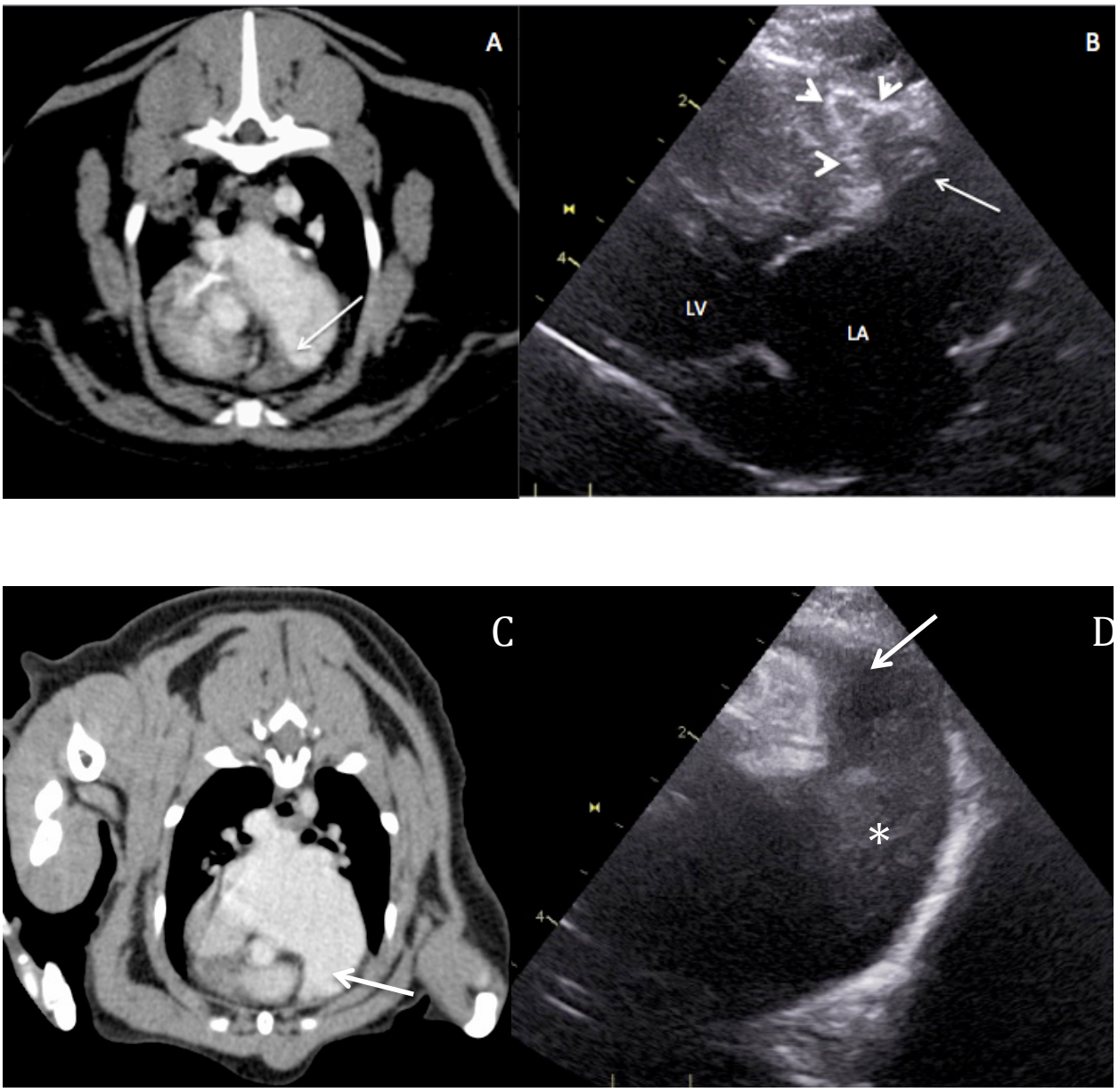


Fig. 3. Transverse CTA (A) of a patient with a dilated left atrium and left auricle with a large filling defect (presumed clot) (white arrow) occupying most of the left auricle. (B) The corresponding oblique left apical parasternal long-axis echocardiographic image of the left auricle with corresponding clot that is similar in appearance conforming to and occupying most of the left auricle. The white arrowheads outline the external margins of the left auricle. LA=left atrium, LV=left ventricle. The second set of images (C,D) is of a patient with severe left atrial enlargement and only smoke identified on echo. Transverse thoracic CTA (C) and oblique left apical parasternal long-axis view of the left auricle (D) with severely dilated left atrium and left auricle with no filling defects noted within the left auricle (white arrow). The asterisk highlights the smoke within the left atrium.

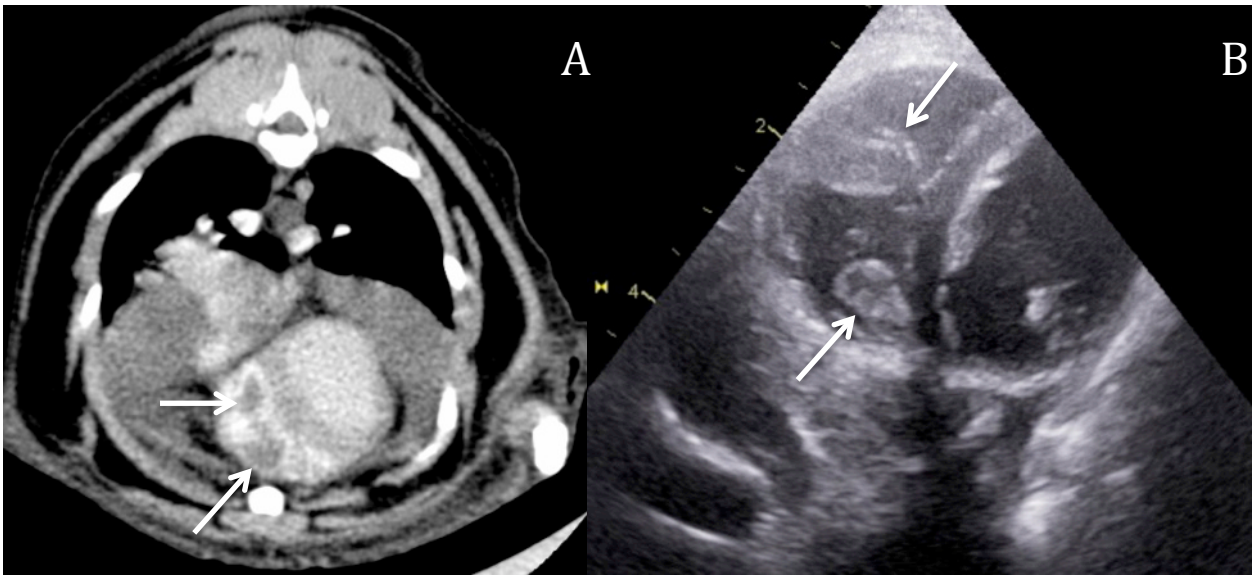


Fig. 4. Transverse CTA (A) of the thorax showing the two well defined irregularly marginated filling defects (clots confirmed on necropsy) (white arrows) within the right ventricle. Right parasternal short axis view at the right ventricular outflow tract showing the two rounded well-defined echogenic clots within the lumen of the right ventricle bordering the endocardial surface.

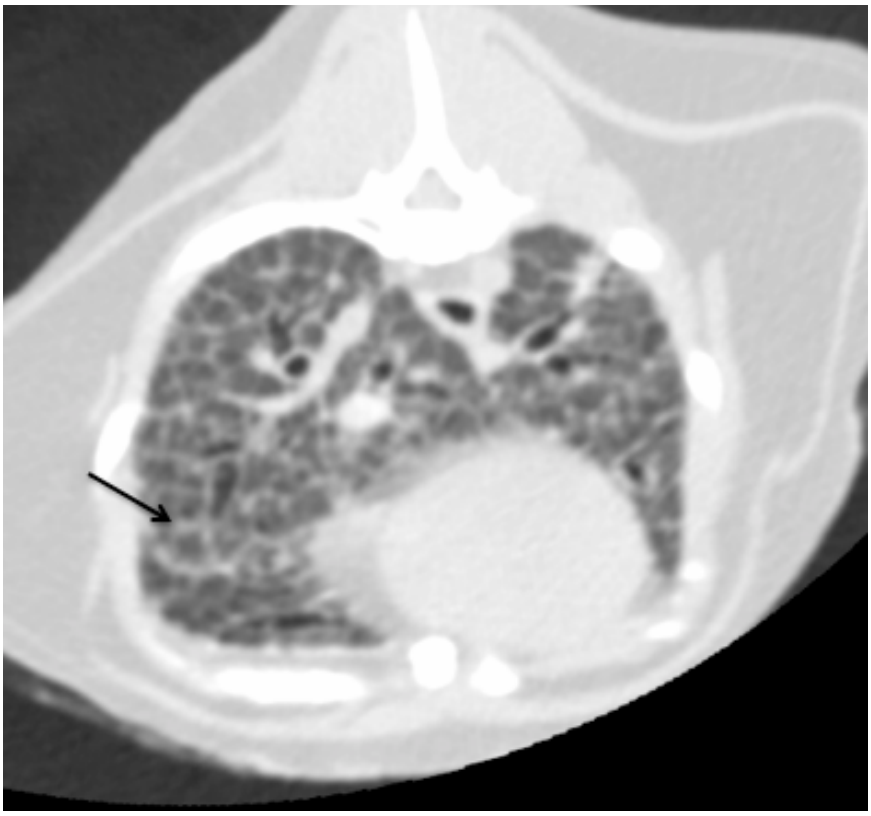


Fig. 5. Transverse noncontrast CT of the thorax at the level of the apex of the heart of a cat with suspect idiopathic pulmonary fibrosis. Note the thickened and hyperattenuating bands outlining the interlobular septa (black arrow) diffusely throughout all of the lung lobes. CT images are in a lung window. WL:-500, WW:1400.

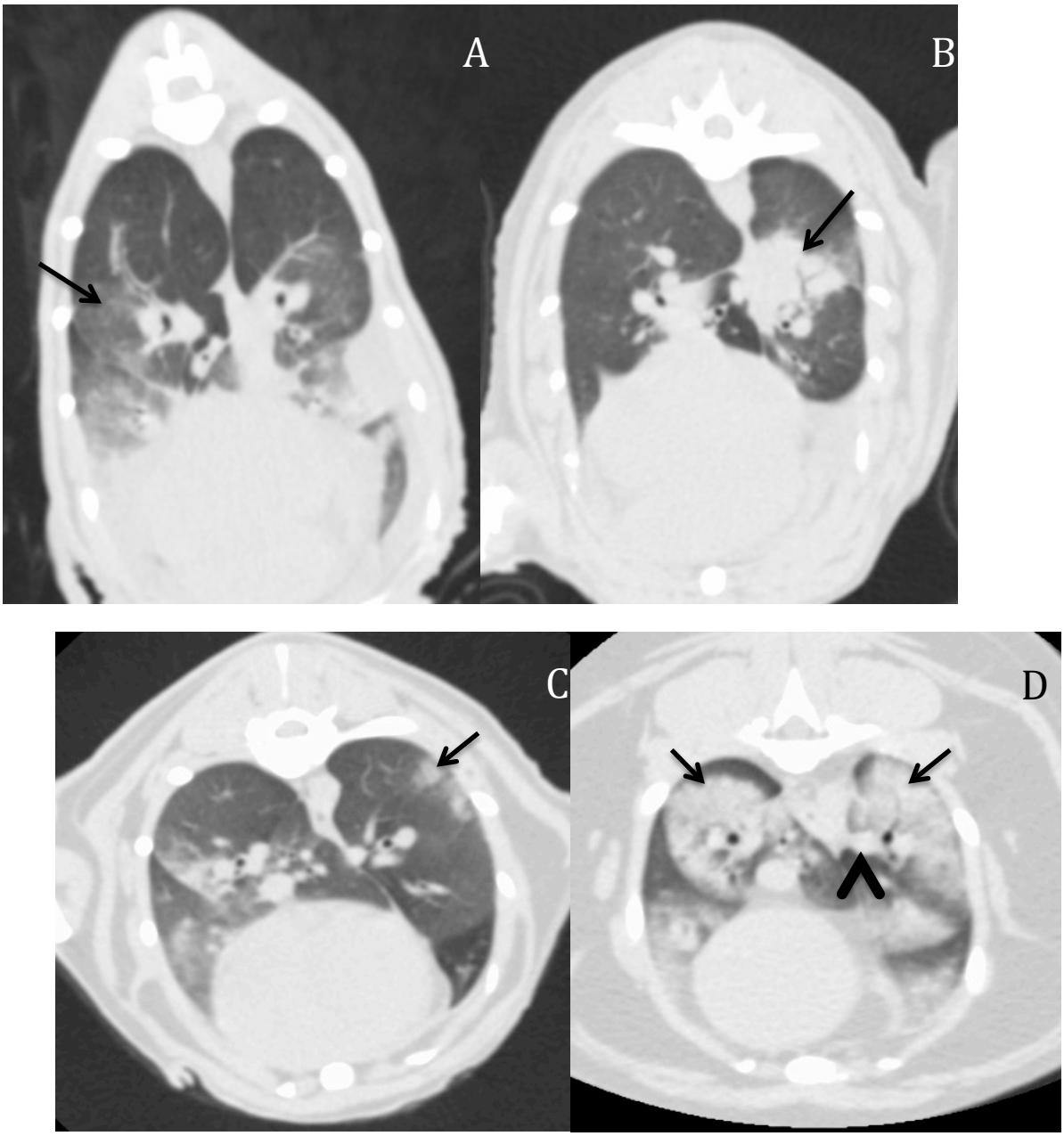
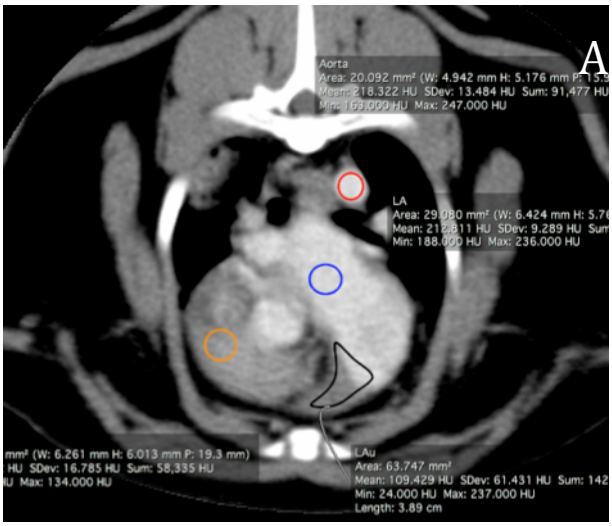


Fig. 6. Transverse noncontrast CT images of the thorax at the level of the mid to caudal heart, all with suspected pulmonary edema (black arrows). (A) There is patchy ill-defined increased attenuation within multiple lung lobes without border effacement of the vessels. (B) Larger focal region of marked irregularly marginated and ill defined increased attenuation with border effacement of the vessels and air bronchograms, almost creating a mass like appearance within the left caudal lung lobe. (C) Focal ill defined nondependent increased attenuation within the periphery of the left caudal lung lobe. (D) Bilateral marked patchy alveolar pattern within the caudal lung lobe centered on the caudal lobar vessels but also ventrally located. Pulmonary venous congestion is present in all images (only delineated in the final image (D) by a black arrowhead). WL:-500, WW:1400.



Fig. 7. Reformatted dorsal plane CTA image of the caudal abdomen showing a well-defined contrast filling defect (white arrow) within the caudal descending aorta that extends into the external and internal iliac arteries.



B

index	Aorta mean	RA mean	LAu mean	LA mean
0	64.098648	47.351051	54.349472	60.152073
1	47.474937	51.281284	52.724567	54.563972
2	65.596664	48.852715	56.490902	60.316498
3	44.767704	50.993912	55.426338	52.732887
4	61.287987	44.687157	58.572895	60.159374
5	42.408119	45.485603	54.225464	53.420879
6	66.144791	40.751381	56.789646	60.31818
7	49.29356	59.562019	56.702541	54.056114
8	68.117744	69.74086	59.241611	60.65657
9	50.863968	86.997787	52.918518	53.51403
10	60.946701	83.270203	55.484501	59.564526
11	51.509151	82.838867	59.323086	62.773293
12	61.630867	80.388702	59.302334	77.169472
13	73.780434	69.967896	59.065334	93.537605
14	76.77327	69.270767	60.97361	109.381599
15	103.37867	67.139542	63.749424	128.419189
16	101.768494	71.021591	60.643093	134.398987
17	132.741455	78.799553	62.4617	140.632431
18	122.647583	90.146736	64.734306	132.391144
19	136.598251	94.041527	68.608772	135.723907
20	129.361191	99.101883	73.094292	135.439392
21	135.108994	103.269104	76.782219	134.898438
22	141.470169	105.342751	77.759155	135.7211
23	128.45665	101.460693	76.582115	138.689117
24	142.017502	98.321709	79.738663	159.176788
25	134.920456	108.236992	78.17115	167.1577
26	156.097855	107.184944	82.260826	178.320999
27	157.44072	105.590256	83.656418	182.421448
28	170.514725	117.234222	87.994621	188.090363
29	182.110611	122.312851	92.752754	191.578568
30	178.737473	127.377632	91.792717	196.324356
31	193.412109	118.364891	104.543678	205.685181
32	186.049316	123.231468	99.628746	207.812012
33	205.150375	122.331665	113.186783	212.298538
34	198.895004	116.590805	107.752762	209.113922
35	211.418457	109.742538	117.154747	214.489899
36	209.194901	101.84108	112.04689	211.379333
37	215.967346	94.287926	119.416084	212.744675
38	217.636032	86.7201	117.077629	211.31987
39	216.949875	76.538208	124.726364	209.828278

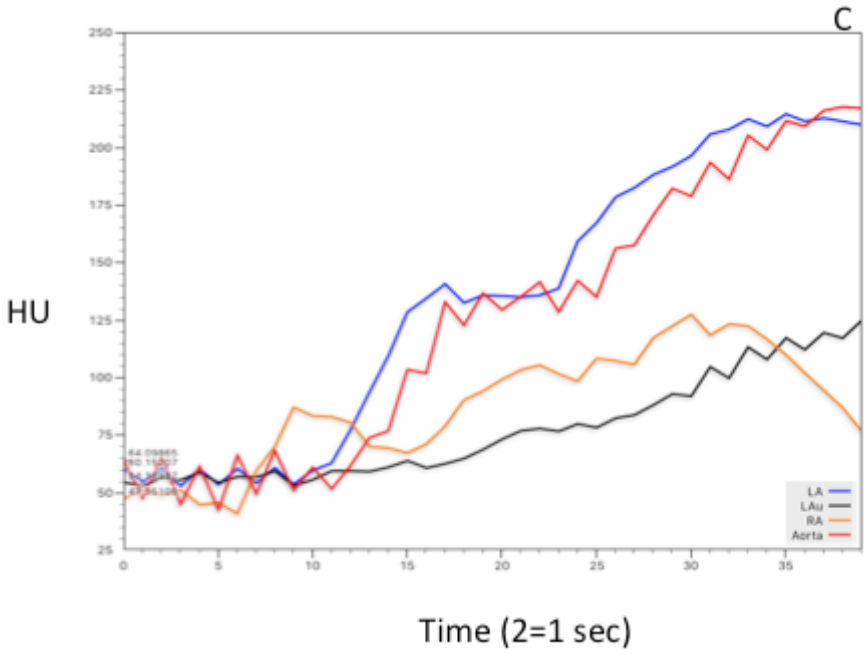


Fig. 8. (cont.)

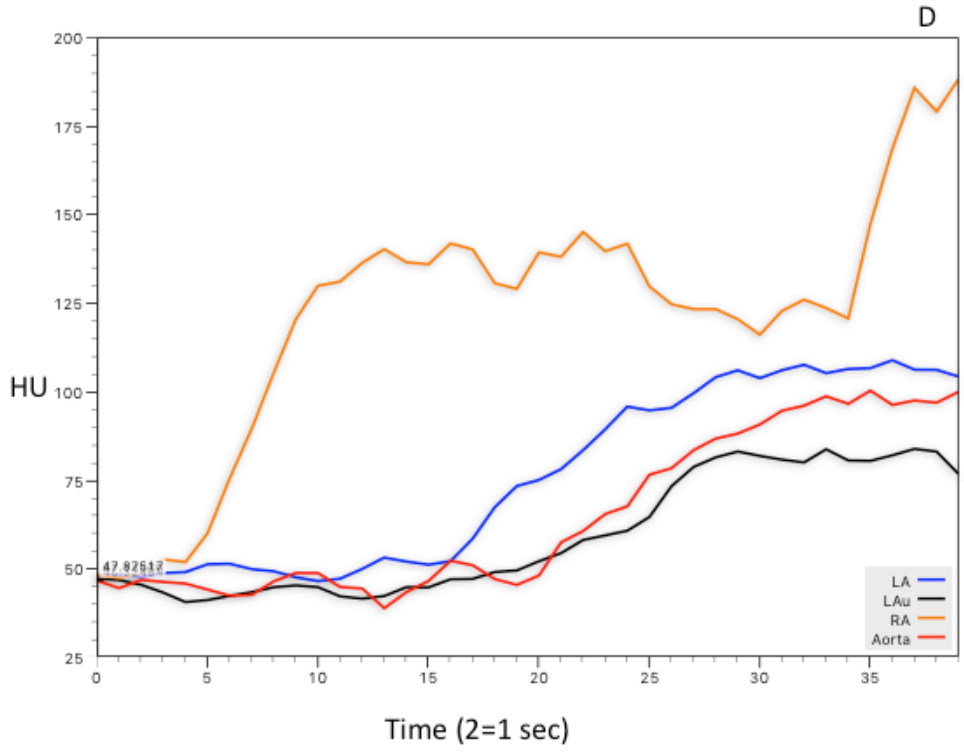


Fig. 8. (cont.) (A) Regions of interest placed within the heart on a transverse dynamic CTA image. Very similar ROI's were placed in all patients. Time attenuation curves (TAC) represented numerically (A,B) and graphically (C) in a patient with a clot. In this patient you can see that the left Auricle (Lau – black line) is markedly lower in attenuation throughout the curve compared to the left atrium (LA – blue line). (D) TAC of a patient with smoke, note that the left auricle is closer matching that attenuation of the left atrium, but slightly lower.

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