**Increased IGF-1 concentrations in a retrospective population of non-diabetic cats diagnosed with hypertrophic cardiomyopathy.**

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**Abstract**

Objectives: The aim of the study was to document whether a proportion of non-diabetic cats with left ventricular hypertrophy (LVH) previously diagnosed with hypertrophic cardiomyopathy (HCM) have elevated circulating insulin like growth factor-1 (IGF-1) concentrations.

Methods: A retrospective analysis of residual blood samples obtained at the time of echocardiographic diagnosis of HCM from a population of 60 non-diabetic cats were analysed for circulating IGF-1 concentrations using a validated radioimmunoassay and compared to a control group of 16 apparently healthy cats without LVH. Clinical and echocardiographic data for cats with IGF-1 >1000 ng/mL were compared to those <800 ng/mL.

Results: 6.7% (95% CI: 1.8 – 16.2%) of cats with HCM had an IGF-1 >1000ng/mL. Prevalence of IGF-1 >1000ng/mL in the control group was zero.

Conclusions and Relevance: A small proportion of non-diabetic cats previously diagnosed with HCM had an IGF-1 concentration at a level that has been associated with feline hypersomatotropism (fHS) in the diabetic cat population. Further prospective research is required to confirm or refute the presence of fHS in non-diabetic cats with LVH and increased IGF-1.

**Introduction**

Diagnosis of hypertrophic cardiomyopathy (HCM), as a primary condition, relies on accurately screening for and the ruling out of conditions that may cause an HCM phenotype.1 An HCM phenotype may be caused by a small number of known disorders in cats; examples include fixed aortic stenosis, infiltrative myocardial disease, hyperthyroidism, systemic hypertension, transient myocardial thickening, myocarditis and hypersomatotropism. 1,2,11,3–10 HCM, as a primary condition, has an average prevalence of 15%, with increasing prevalence occurring with age.

Feline hypersomatotropism (fHS), which causes the clinical syndrome of feline acromegaly, is increasingly recognized as an important endocrinopathy in cats and it may be present in approximately 17-25% of diabetic cats.12,13 fHS is typically associated with the concurrent presence of diabetes mellitus (DM),12,14,15 whereas fHS in non-diabetic cats has only been reported in a small number of cases.16,17 Conversely, in people, hypersomatotropism in the absence of DM is common. 18,19 Furthermore, the presence of growth hormone induced LVH is also recognized in patients without concurrent DM. 20–22

LVH is commonly seen in diabetic cats with fHS;23,24 importantly this seems to be a reversible cause of cardiac remodeling in most cases following hypophysectomy.10 This association of LVH to fHS has only been documented in cats with the typical phenotype of fHS, i.e. fHS with concurrent DM. The prevalence of fHS in cats without DM has not been assessed and no current studies have explored the possibility of fHS in non-diabetic cats with LVH.

The aim of this study was to measure IGF-1 in stored serum or plasma samples of non-diabetic cats previously diagnosed with HCM using a validated radioimmunoassay (RIA),12 and to compare the prevalence of IGF-1 concentrations >1000 ng/mL, a cut-off associated with a high probability of fHS in diabetic cats,12 to a control population of apparently healthy cats without LVH. We hypothesized that we would detect a number of non-diabetic cats previously diagnosed with HCM with IGF-1 concentrations above a threshold that could raise a tentative suspicion for fHS and provide grounds for further study. In addition, we hypothesized that clinically healthy cats without LVH would not have IGF-1 concentrations >1000ng/mL.

**Materials and Methods**

*Study Population*

A population of non-diabetic cats previously diagnosed with HCM and with a banked residual blood sample, obtained at the time of echocardiographic diagnosis, were selected via review of computerised patient records from client owned cats. This population had been referred to either of two veterinary teaching hospitals; The Queen Mother Hospital for Animals, Royal Veterinary College and Langford Vets, University of Bristol over a period spanning five-years (2012 – 2017). A group of apparently healthy control cats, without LVH on echocardiography, were recruited from a geriatric cat health clinic, performed at two first-opinion practices (a geriatric cat research outreach clinic run weekly at PDSA Bow and Blue Cross Victoria, London) over an 8-week period in 2013 – 2014 where blood samples were collected at the same time that echocardiography was performed. Analysis of IGF-1 concentrations from the stored serum/plasma samples from both groups was performed in 2017. Ethical approval by both institutions was granted (URN 2017 1734-2 and VIN/17/041 numbers, respectively) and, in both institutions, owner permission for the use of residual blood samples is obtained at the time the initial blood sample is taken.

*Inclusion Criteria*

To be included, a residual blood sample (either serum or plasma) stored at -80oC for no longer than the five-year period stated above had to be available. All cats must have had a documented history, physical examination, echocardiographic examination performed by a cardiology Diplomate or resident under direct supervision using a standard protocol, 25 non-invasive blood pressure measurement (NIBP) and, if over the age of seven years, a total thyroxine (TT4) result available for review. Echocardiographic diagnosis of control and HCM cats was confirmed by a cardiology Diplomate (KB, JRP, XNC) according to current consensus guidelines.1

*Exclusion Criteria*

Cats were excluded if there was documented evidence of disorders likely to result in secondary LVH: specifically, hyperthyroidism, systemic hypertension or congenital heart disease such as aortic stenosis. Hyperthyroidism was excluded based on absence of compatible historical or physical examination findings in all cats (unexplained weight loss, increased appetite, hyperactivity, behavioral changes or palpable goiter) with the additional requirement of total thyroxine (T4) <40nmol/L (Immulite© 1000, Siemens Healthineers, Surrey, UK, (laboratory reference interval of 19-65 nmol/L) in all cats over 7-years-old.26 Systemic hypertension was defined as at least three consecutive measurements of systolic NIBP exceeding 160 mmHg as per current guidelines.27 In cases with equivocal results (140-159 mmHg) the presence of retinal changes compatible with hypertensive retinopathy were used as a further exclusion criterion. DM was excluded based upon review of clinical records for clinical signs and clinicopathologic data consistent with DM. Therefore, patients with evidence of unexplained polyuria, polydipsia or polyphagia were excluded as were patients with unexplained weight loss despite normal or increased appetite. Additionally, cats with repeatable hyperglycemia (>113 mg/dL) or glycosuria and/or serum fructosamine >400 μmol/L were assumed to be diabetic and were also excluded.28

*IGF-1 Measurement*

Total IGF-1 concentrations were measured using a previously validated, commercially available RIA (Nationwide Specialist Laboratories, Cambridge, UK).12,24 A cut-off of >1000 ng/mL has previously been shown to result in a 95% positive predictive value for fHS using this particular assay when used in diabetic cats.12 Although the cats in this present study were non-diabetic, values above this cut-off were considered elevated. Cats with results that may be considered equivocal (800-1000 ng/mL) were not included in statistical comparisons.12

*Patient Data*

Retrospective medical data were entered into an electronic database for analysis (Microsoft Excel for Mac, Version 16.5: Microsoft Corporation, Washington USA). Patient details (age, weight, breed and sex), physical examination findings (heart rate, resting respiratory rate, body weight, grade of heart murmur and presence or absence of arrhythmia and gallop sound) were recorded. Patients were classified as being in congestive heart failure (CHF) based on a combination of compatible historical, physical examination or ancillary test findings that would suggest pulmonary oedema/pleural effusion with concurrent cardiac changes making CHF the most likely diagnosis. For example, dyspnea in the presence of an enlarged left atrium (defined as a left atrial to aortic ratio, measured on a short axis view (LA:Ao) >1.5 and/or left atrial diameter (LAD), measured from a right parasternal long-axis view in the last frame before mitral valve opening LAD >16.0mm), point of care ultrasound for evidence of B-lines and/or pleural fluid with left atrial enlargement, or thoracic radiography demonstrating an alveolar pattern and or pleural effusion with cardiomegaly and/or pulmonary vessel congestion.29–31 A diagnosis of feline arterial thromboembolism (ATE) was recorded based upon evidence of acute paresis or paralysis in one or more limbs, accompanied by limb pain, pulselessness or pallor in an affected limb or limbs; in combination with a compatible clinical history.32 Standard echocardiographic measurements were included in the database for analysis.

*Outcome Data*

For the cats with IGF-1 >1000 ng/mL the referring practices were contacted to determine if any evidence of DM or fHS, defined as compatible clinical, morphological or clinicopathologic signs, developed following the diagnosis of HCM.12 The current status of the patient as alive/deceased/unknown was determined, along with the cause of death, if applicable. In addition, the time since diagnosis of LV hypertrophy and blood sampling was recorded based on the date of the last contact in the clinical records.

*Statistical Analysis*

Analysis was performed using commercially available software (IBM SPSS Statistics, Version 26, Chicago, USA). Data were assessed graphically and by Shapiro-Wilk tests for normality. Data is represented as median (range) due to the majority of data having skewed distribution. The proportion of cats with IGF-1 >1000 ng/mL was calculated in both HCM and control groups, and confidence intervals (CI) calculated (http://www.sample-size.net/confidence-interval-proportion/). HCM cats with an IGF-1 >1000 ng/mL were compared with those with IGF-1<800 ng/mL, to see if any associations could be made with an elevated IGF-1. Categorical variables were compared using χ2 or Fisher’s Exact tests. Continuous variables were compared using Mann-Whitney U or an independent samples T-test. Significance level was set at 5% (*P* <0.05).

**Results**

*Population Characteristics*

Records and blood samples of 60 cats with HCM meeting the inclusion criteria were available. Median age was 8 years (1-19 years). Pedigree breeds were represented in 20% (n=12) of cats: consisting of three British Shorthair (5%), three Persian (5%), two British Blue (3%), and one each of the following: Devon Rex, Sphynx, Maine Coon and Russian Blue. The remaining 80% (n=48) of cats were non-pedigree. 63% (n=38) of cats were male and 36% (n=22) were female. All but one cat (female) was recorded as neutered. The median bodyweight for all cats in the study was 4.47 kg (3.10-8.80 kg). A summary of clinical and echocardiographic data for cats with HCM and the healthy controls, are summarized in Table 1. Table 2 details the medications being received by the 60 cats diagnosed with HCM in this study.

Table 1: *Population characteristics, clinical presentation data and echocardiographic data for healthy control cats with no evidence of left ventricular hypertrophy.*

|  |  |  |
| --- | --- | --- |
|  | **Cats diagnosed with HCM** | **Healthy Control Cats** |
| **Number** | 60 | 16 |
| **Age (years)** | 8.0 (1.0 – 19.0) | 13.2 (10.0 – 20.0) |
| **Weight (kg)** | 4.55 (3.13 – 8.83) | 4.13 (3.05 – 6.46) |
| **IGF-1 (ng/ml)** | 501 (25 - 1179) | 439 (207 – 681) |
| **Pedigree (number)** | 10 (16.7%) | 0  |
| **Male** | 38 (63.3%) | 8 (50%) |
| **Heart murmur grade III or louder** | 30 (50%) | 1 (6%) |
| **Arrhythmia** | 16 (26.7%) | 0  |
| **LV max thickness (mm)** | 7.0 (6.0 – 12.6) | 5.0 (4.1-5.8) |
| **LVIDd (mm)** | 14.0 (8.3 – 28.0) | 14.4 (11.3 – 16.9) |
| **LA:Ao ratio** | 1.54 (1.02 – 3.61) | 1.22 (1.01 – 1.39) |
| **LA diameter (mm)** | 17.00 (2.00 – 30.00) | 13.94 (11.20 – 17.44) |

*Table 1: Population characteristics, clinical presentation data and echocardiographic data for cats with HCM vs. healthy control cats with no evidence of left ventricular hypertrophy. Values displayed as median (range). Categoric variables are displayed as a number (percentage) of cats with the clinical sign or echocardiographic criteria. IGF-1 = insulin-like growth factor-1. LV = left ventricle, LVIDd = left ventricular internal diameter in diastole, LA:Ao = left atrium to aortic ratio in a short axis view.*

*Table 2: Cardiac medications prescribed to cats diagnosed with HCM*

|  |  |
| --- | --- |
| **Medications** | **Number of HCM cats receiving medications** |
| Atenolol | 5 (8%) |
| Aspirin | 6 (10%)  |
| Benazepril | 5 (8%) |
| Benazepril + Spironolactone combination | 2 (3%) |
| Clopidogrel | 10 (17%) |
| Diltiazem | 1 (2%) |
| Enalapril | 1 (2%) |
| Frusemide | 12 (20%) |
| Hydrochlorothiazide | 2 (3%) |
| Pimobendan | 5 (8%) |
| None | 37 (62%) |

*Table 2: Cardiac medications prescribed to cats with HCM are displayed as number (percentage)*

*Distribution of IGF-1 results*

Of the cats diagnosed with HCM, IGF-1 >1000 ng/mL was found in 6.7% (n=4, 95% CI: 1.8 – 16.2%) of cases. Three cats had an IGF-1 800-1000ng/mL, and were excluded from further analysis. The remainder (88%, n=53) had an IGF-1 <800 ng/mL. The distribution of IGF-1 results across this population as well as the healthy control cats are shown in Figure 1. Of the healthy control cats, all samples measured <800 ng/mL.

**[Insert Figure 1]**

*Associations between clinical variables and IGF-1 results in cats diagnosed with HCM*

Population data for HCM cats with IGF-1 >1000 ng/mL, IGF-1 <800 ng/mL and IGF-1 800-1000 ng/mL are presented in Table 3. Comparisons were performed between cats with IGF-1 >1000 ng/mL and cats with IGF-1 <800 ng/mL only. HCM cats with IGF-1 >1000 ng/mL were significantly heavier, had larger LA:Ao and poorer LA function than those with IGF-1 <800 ng/mL (Table 3). A greater proportion of cats with IGF-1 >1000 ng/ml also presented with CHF compared to those with IGF-1 <800 ng/mL (Table 3). No other significant differences in population, clinical and echocardiographic data were found.

*Table 3: Population characteristics, clinical presentation data and echocardiographic data for cats according to circulating IGF-1 concentration (IGF-1 >1000 ng/mL, significant elevation; IGF-1 <800 ng/mL, likely normal; and IGF-1 800-1000 ng/mL, equivocal)*

|  |  |  |
| --- | --- | --- |
|  | **Circulating IGF-1 concentration** | ***P* value for comparisons of cats with IGF-1 <800ng/mL vs. IGF-1 >1000ng/mL.** |
| **IGF-1 <800 ng/mL** | **IGF-1 >1000 ng/ml** | **IGF-1 800-1000 ng/mL** |
| **Number** | 53 | 4 | 3 | n/a |
| **Age (years)** | 8.0 (1.0-19.0) | 8.5 (8.0-9.0) | 7.0 (2.0-11.0) | 0.730 |
| **Weight (kg)** | 4.63 (3.13-6.67) | 5.50 (5.40-5.50) | 4.70 (4.45 – 6.00) | 0.019\* |
| **IGF-1 (ng/ml)** | 462 (25 – 779) | 1142 (1106-1179) | 877 (828 – 879) | n/a |
| **Pedigree (number)** | 11 (20%) | 1 (25%) | 0 | 0.669 |
| **Male** | 32 (60%)  | 4 (100%) | 3 (100%) | 0.332 |
| **HR (beats/min)** | 180 (100-260) | 170 (160-220) | 180 (160 – 180) | 0.736 |
| **RR (breaths/min)** | 34 (20-66) | 33 (22-44) | 48 (28 – 56) | 0.693 |
| **Heart murmur grade III or louder** | 9 (17%) | 0 | 2 (67%) | 0.102 |
| **CHF** | 14 (26%) | 4 (100%) | 2 (67%) | 0.006\* |
| **ATE** | 12 (23%) | 3 (75%) | 1 (34%) | 0.135 |
| **Arrhythmia** | 12 (23%) | 3 (75%) | 1 (34%) | 0.135 |
| **DLVOTO=yes** | 23 (43%) | 0 | 3 (100%) | 0.140 |
| **DRVOTO=yes** | 9 (17%) | 0 | 0 | 0.497 |
| **LV max thickness (mm)** | 7.4 (6.0-12.6) | 6.9 (6.0-7.8) | 7.1 (6.0 – 8.8) | 0.467 |
| **LVIDd (mm)** | 13.4 (8.3-19.2) | 14.5 (12.0-17.0) | 14.1 (11.8 – 14.2) | 0.140 |
| **LVFS%** | 50.5 (22.5-78.6) | 38.8 (23.0-78.0) | 59.50 (49.97 – 62.00) | 0.795 |
| **LA:Ao ratio** | 1.48 (1.02-2.89) | 3.13 (2.64-3.61) | 2.10 (1.22 – 3.06) | 0.0077\* |
| **LAFS%** | 25 (4-47) | 10 (3.0-17.0) | 22 (11 – 33) | 0.0093\* |

*Table 3: Population characteristics, clinical presentation data and echocardiographic data for cats according to circulating IGF-1 concentration (IGF-1 >1000 ng/mL, significant elevation; IGF-1 <800 ng/mL, likely normal; and IGF-1 800-1000 ng/mL, equivocal). Values displayed as median (range). Categoric variables are displayed as number (percentage) of cats with the clinical sign or echocardiographic criteria compared to their respective group, i.e. not as a percentage of the total population. Cats with IGF-1 >1000 ng/mL and <800 ng/mL were compared statistically, ‘\*’ is used to indicate statistically significant differences (P<0.05) between these groups. Cats with IGF-1 800-1000ng/mL were excluded from statistical analysis. IGF-1 = insulin-like growth factor-1, HR = heart rate, RR = respiratory rate, CHF = congestive heart failure, ATE = arterial thromboembolism, DLVOTO = dynamic left ventricular outflow tract obstruction, DRVOTO = dynamic right ventricular outflow tract obstructions, LV = left ventricle LVIDd = left ventricular internal diameter in diastole, LVFS% = left ventricular fractional shortening, LA:Ao = left atrium to aortic ratio in a short axis view, LAFS% = left atrial fractional shortening*

*Outcomes of cats with IGF-1 >1000 ng/mL*

One cat was euthanased nine days following diagnosis of HCM, because of suspected recurrent ATE. Another cat died three-months post diagnosis, with no further information available related to the exact cause of death. The other two cats had unknown status with the last known contact following diagnosis being one month for one cat and two years for the other cat. None of these cats displayed any sign of DM or fHS in their clinical records up to the date of their last contact.

**Discussion**

In our population of cats diagnosed with HCM, 6.7% of cases had a circulating IGF-1 >1000 ng/mL (95% CI: 1.8 – 16.2%), none of the cats in the apparently healthy control group had an IGF-1 >1000ng/mL. This highlights that a small percentage of non-diabetic cats diagnosed with HCM, had IGF-1 in a range that would be consistent with fHS in a diabetic cat. The presence of fHS in these cats is unknown and warrants further investigation but if present, would imply that some cats with LVH could be misclassified as primary HCM.

Measurement of IGF-1 >1000ng/mL, using RIA, is reported to have good sensitivity for fHS.33 The IGF-1 assay used in this study has previously been validated and shown to have a PPV of 95% for fHS in the diabetic cat population using this cut off.12 Given there is some evidence in the veterinary literature of non-diabetic cats with fHS,16,17 it is possible that in the cats with IGF-1 >1000ng/mL, fHS may, at least in part, have had an impact on their wall thickness, rather than HCM being solely responsible for the LVH. However, confirmation of the diagnosis of fHS in the cats with an IGF-1 >1000ng/mL would be needed to provide definitive support for this hypothesis. This would require advanced intra-cranial imaging, such as CT or MRI, or a post mortem examination to document pituitary acidophil hyperplasia.12,24,34 This was not possible due to the retrospective nature of this study. Such studies would be warranted given that if there is a population of non-diabetic cats with fHS induced cardiomyopathy this may be a partially or fully reversible cause of LVH.14

Caution should be applied in extrapolating the PPV of our assay from diabetic cats to the non-diabetic cats in our study, given PPV is affected by disease prevalence. Although there are case reports of non-diabetic cats with fHS and not all diabetic fHS cats exhibit the typical phenotype of poor glycaemic control, the prevalence of fHS in non-diabetic cats remains unknown and therefore the correct IGF-1 cut-off for a presumptive diagnosis of fHS in non-diabetic cats has not been determined. The cats in this study with an IGF-1 >1000ng/mL cannot, therefore, be assumed to have fHS without further diagnostic intervention.16,17,24,24 Furthermore, if these cases did have fHS we cannot definitively conclude that it was responsible for their LVH. The cats with IGF-1 >1000ng/mL in our study were 8.0-9.0 years old, an age range that has a relatively high prevalence of HCM; HCM and fHS could be present as concurrent but independent diseases in cats of this age range, both of which could have an impact on ventricular wall thickness.25

Cats with IGF-1 > 1000ng/mL were found to be in congestive heart failure and most (3/4) had concurrent ATE. The presence of larger LA:Ao and reduced LAFS% may also reflect a more advanced state of cardiac disease.29 However, the reader is cautioned against drawing conclusions on any causal relationship between changes in IGF-1 and the progression of cardiac disease due to the small number of cases. This could be explored in future studies.

Limitations of this study are inherent to the studies design. The HCM population consisted of cats from two referral centers in the UK and therefore may not reflect the wider cat population. Furthermore, these cats represent a selected and small proportion of cats with HCM entering the hospitals and may not reflect these center’s HCM cohorts as a whole. The control group was relatively small and unfortunately was not age matched. It was also from a general practice population; this is in contrast to the HCM cats which were from a referral population. These limitations reflect difficulties in recruiting healthy control populations, and were unavoidable. Ageing is associated with reduced IGF-1 in cats, but this is a limited effect and would be unlikely to reduce an IGF-1 result to a degree that would be clinically relevant in ruling in or out fHS.35 Therefore, it is unlikely that lack of age-matching in this study would change the conclusions we have drawn from our data. Since this was a retrospective study, we were reliant on clinical records and diagnostic testing ordered by clinicians at the time, which may have been incomplete, inaccurate or subject to unknown confounding bias. Additionally, the diagnostic approach was not standardised apart from the inclusion criteria of echocardiography performed without sedation, standardisation of echocardiography technique and a blood sample collected at the time of echocardiography. Sample handling at the time of collection or later storage may have affected measurable IGF-1 concentration. Finally, the effect of long-term storage on feline blood samples for IGF-1 measurement is currently unknown and could lead to falsely decreased or increased IGF-1 results.

**Conclusions**

In a cohort of cats previously diagnosed with HCM, 6.7% (95% CI: 1.8 – 16.2%) were found to have IGF-1 >1000 ng/mL, conversely no cats in a healthy control population without LVH had IGF-1 concentrations over 800 ng/mL. Future prospective studies are warranted to determine whether or not these cats with IGF-1 >1000ng/mL have fHS and if this is the case whether their LVH is a direct result of fHS or represents concurrent HCM. Alternatively, these IGF-1 elevations may be a result of other factors that are not yet completely understood.

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None

**Author Note**

An abstract of the current study under the title “Prevalence of hypersomatotropism in non-diabetic cats with left ventricular hypertrophy - a silent and curable phenocopy for hypertrophic cardiomyopathy” was presented at ECVIM-CA Congress 2018.

**Conflict of interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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**Ethical approval**

This work involved the use of non-experimental animals (owned or unowned) and procedures that differed from established internationally recognised high standards (‘best practice’) of veterinary clinical care *for the individual patient*. The study therefore had ethical approval from an established committee as stated in the manuscript.

**Informed Consent**

Informed consent for use of residual blood samples was obtained from the owner or legal custodian of all animal(s) described in this work at the time of sampling for the procedure(s) undertaken.

No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required

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