

# A Randomized Study Assessing the Effect of Diet in Cats with Hypertrophic Cardiomyopathy

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**Background:** Diet might influence progression of hypertrophic cardiomyopathy (HCM).

**Objective:** To investigate whether diet composition could alter clinical, biochemical, or echocardiographic variables in cats with HCM.

**Animals:** Twenty-nine cats with HCM (International Small Animal Cardiac Health Council stage 1b) examined at a university teaching hospital.

**Methods:** Randomized, placebo-controlled trial. After physical examination, echocardiogram, and blood collection, cats were randomized to 1 of 3 diets, which varied in carbohydrate and fat content and ingredients. Measurements were repeated after 6 months.

**Results:** There were no significant differences among the 3 groups at baseline. After 6 months, there were no significant changes in the primary endpoints, left ventricular free wall (Group A,  $P = .760$ ; Group B,  $P = .475$ ; Group C,  $P = .066$ ) or interventricular septal thickness in diastole (Group A,  $P = .528$ ; Group B,  $P = .221$ ; Group C,  $P = .097$ ). Group A had significant increases in BUN ( $P = .008$ ) and cholesterol ( $P = .021$ ), while Group B had significant increases in BUN ( $P = .008$ ), cholesterol ( $P = .007$ ), and triglycerides ( $P = .005$ ), and significant decreases in NT-proBNP ( $P = .013$ ) and hs-troponin I ( $P = .043$ ). Group C had significant decreases in body weight ( $P = .021$ ), left atrial dimension ( $P = .035$ ), interventricular septal thickness in systole ( $P = .038$ ), and liver enzymes ( $P = .034$ – $.038$ ).

**Conclusions and Clinical Importance:** These data suggest that diet might influence some clinical, biochemical, and echocardiographic variables in cats with HCM.

**Key words:** Cardiomyopathy; Congestive heart failure; Nutrition.

Gene–nutrient interactions might play a role in the wide phenotypic variation seen in hypertrophic cardiomyopathy (HCM) in both people and cats. This area of research is relatively new, but there is some evidence suggesting that diet or nutrients can modify phenotypic expression of cardiomyopathy in genetically predisposed individuals. In 1 study,<sup>1</sup> mice with an alpha-myosin heavy chain mutation were fed either a soy- or casein-based diet, and the results showed that males eating the soy-based diet developed more severe heart disease compared with those eating the casein-based diet. Another study in spontaneously hypertensive heart failure (SHHF) rats<sup>2</sup> showed that rats fed a test diet (higher in carbohydrate and sucrose and lower in protein) developed higher blood pressure, glucose, inflammatory mediators, and left ventricular free wall in diastole (LVWd), and also an accelerated development of congestive heart failure (CHF) and death compared with rats eating the control diet. Finally, in a recent study of 275 adult people with HCM, not only was left ventricular mass higher in overweight and obese patients but

## Abbreviations:

2D	2-dimensional
A'	late diastolic myocardial velocity
A	late diastolic velocity of mitral inflow
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCS	body condition score
CHF	congestive heart failure
DHA	docosahexaenoic acid
E'	early peak diastolic myocardial velocity
E	early diastolic velocity of mitral inflow
EPA	eicosapentaenoic acid
HCM	hypertrophic cardiomyopathy
HOMA	homeostasis model assessment
hs-troponin I	high-sensitivity cardiac troponin I
ISACHC	International Small Animal Cardiac Health Council
IVRT	isovolumic relaxation time
IVSd/s	interventricular septal thickness in diastole/systole
LA	left atrium
LVIDd/s	left ventricular internal dimension in diastole/systole
LVWd/s	left ventricular free wall thickness in diastole/systole
NT-proBNP	N-terminal pro B-type natriuretic peptide

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obesity also was an independent predictor of progression to New York Heart Association Class III or IV.<sup>3</sup> While the authors<sup>3</sup> and the corresponding editorial<sup>4</sup> attributed obesity to being a secondary effect of HCM (ie, because people with HCM are less likely to be physically active, they are more likely to become obese), it is possible that the obesity contributed to a worse phenotypic expression of the disease and that this hastened disease progression.

The relationship between dietary factors and cardiovascular phenotype in cats with HCM has not been reported. However, there currently is a large variety of

commercial cat foods available from which consumers can choose. These diets vary in ingredients and nutrient profiles, including macronutrients (ie, protein, fat, carbohydrate), micronutrients (eg, essential vitamins and minerals), and other nutrients that also can have nonnutritional effects (eg, omega-3 fatty acids, antioxidants). It is not yet known whether this wide spectrum of dietary properties found in commercial cat foods could alter phenotypic expression of disease in cats with HCM, but identifying methods for slowing progression of HCM would be useful. If modification of diet could be shown to alter progression of disease, time to CHF, survival time, or quality of life, this would be beneficial for the cats with this common disease.

To begin to investigate the role of diet in modifying disease, the objective of this randomized study was to investigate whether diet composition could alter clinical, biochemical, or echocardiographic variables in cats with HCM, but with no clinical signs.

## Materials and Methods

This randomized parallel-design study was approved by the Tufts Cummings School of Veterinary Medicine Clinical Studies Review Committee. Cats with HCM were recruited from clients, staff, and students of Tufts Cummings School of Veterinary Medicine. All owners signed an informed consent form before enrolling cats in the study. To be eligible, cats had to have typical echocardiographic features of HCM (see below) and be without clinical signs for heart disease (International Small Animal Cardiac Health Council stage 1b).<sup>5</sup> Cats were excluded if they had important concurrent disease (eg, cancer, diabetes, chronic kidney disease) based on the history, physical examination, and laboratory testing. Physical examination was performed by a board-certified cardiologist and all body condition scores (BCS) and muscle condition scores (MCS) were performed by a single investigator (LMF). Body condition scores were assessed using a 9-point score,<sup>6</sup> while muscle condition was graded as normal, mild muscle loss, moderate muscle loss, or severe muscle loss.<sup>7</sup> Blood pressure was measured by Doppler technique using the mean of 3 systolic measurements. Cats with a mean systolic blood pressure >180 mmHg were considered hypertensive and excluded from the study. A diet history was collected from all cats' owners to determine the specific cat foods provided to the cat, as well as treats, table foods, dietary supplements, and foods used to administer medications. The amount of dry versus canned food was categorized as all dry, mostly dry, half dry and half canned (when approximately 50% of calories were provided by each form of food), mostly canned, and all canned. Dietary sodium content of the cats' usual diet was calculated using manufacturers' information on a mg/100 kcal basis.

Echocardiography (2D, M-mode, and color flow, spectral and tissue Doppler)<sup>8</sup> was performed on all cats. For echocardiography, right parasternal long- and short-axis views were obtained, and left apical 4- and 5-chamber views were also obtained. Left ventricular, left atrial, and aortic M-mode dimensions were measured in right parasternal short-axis views using 2D guidance.<sup>8,9</sup> The 2D left atrial and aortic dimensions were obtained in the right parasternal short-axis view in diastole,<sup>10</sup> and the 2D interventricular septum and left ventricular free wall measurements were obtained in the right parasternal short- or long-axis view of the left ventricle in end-diastole. Cats were diagnosed with HCM if they had either an interventricular septal thickness in diastole

(IVSd) or LVWd >0.6 cm,<sup>11</sup> measured by 2D or M-mode echocardiography and concurrent findings indicative of HCM (ie, some combination of systolic anterior motion of the mitral valve, left atrial enlargement, or increased aortic velocity). In cats in which the E and A waves were fused (n = 2 at baseline and n = 2 at follow-up visits), values for those waves were not used. No medications were changed at the time of starting the study. If a medication change was judged by the cardiologist to be clinically necessary, that change was made and enrollment in the diet study was delayed for at least 8 weeks. In this situation, all baseline measurements (ie, physical examination, echocardiography, laboratory testing, blood pressure) were performed at the time of enrollment in the diet study.

Blood was collected by jugular venipuncture into serum (biochemistry profile, insulin, high-sensitivity troponin I [hs-troponin I], T4 if >6 years of age) and EDTA tubes (N-terminal pro B-type natriuretic peptide [NT-proBNP]). The biochemistry profile (and T4, if performed) was analyzed immediately and the remaining tubes were centrifuged. Serum was frozen at -80°C for batch analysis of insulin<sup>b</sup> and hs-troponin I.<sup>c</sup> Plasma was transferred from the EDTA tube to a protease inhibitor tube, agitated gently, and then the plasma was frozen at -80°C until analysis for NT-proBNP was performed.<sup>d</sup> The homeostasis model assessment (HOMA), a calculation that has been used as an estimate of insulin sensitivity in cats, was calculated using the formula:  $HOMA = [(insulin \times glucose)/22.5]$ .<sup>12</sup>

After ensuring eligibility and baseline assessments, cats were randomized to 1 of 3 diet groups.<sup>e-j</sup> A random number table was developed by 1 investigator (LMF) using a computer-based random number generator. As this was designed as a pilot study, controlled test diets were not formulated for the study, but instead, commercially available foods with the desired properties were selected with the goal of having all 3 diet groups mildly sodium-restricted ( $\leq 100$  mg/100 kcal), but to vary in carbohydrate, fat, and main ingredients (Table 1). For each group, commercially available dry and canned diets were selected that were similar to one another in nutrient profile and ingredients. Cardiologists and all students and other clinicians working with the cats were blinded to the random allocation sequence and diet assignment until the entire study had been completed. Only 1 investigator (LMF) and the owners were aware of the diet assignment and all communications with cat owners regarding diet were made with that 1 investigator to ensure that other clinicians remained blinded. After the initial visit, the owner was instructed to make a gradual change to the new diet over 4-5 days and then to feed only the assigned study diet for the next 6 months. Owners were allowed to provide up to 5% of the cat's total daily caloric intake from low-sodium treats or table food if this had been their usual practice before starting the study and if they kept this practice consistent throughout the study. Owners were instructed to feed an amount to maintain current body weight for the duration of the study. Owners were encouraged to weigh the cat during the study, especially if body weight appeared to be changing, so that adjustment of food amounts could be made. Owners were contacted monthly for progress reports and to ensure adequate food supply. After the study was underway, diets were analyzed for the isoflavones, genestein and daidzein, using HPLC with UV detection as previously described.<sup>13</sup>

At the end of the 6-month period, cats were re-evaluated while still eating the assigned study diet. The same cardiologist evaluated each cat (except in 2 cases in which this was not logistically possible). All baseline laboratory, blood pressure, and echocardiographic measurements were repeated at this second visit.

The 2 primary endpoints for the study were LVWd and IVSd. Secondary endpoints were left atrial dimension and NT-proBNP. However, as a preliminary study, multiple other clinical, echocardiographic, and laboratory variables were evaluated. No interim

**Table 1.** Nutritional profiles for the 3 diet groups. Each diet group had a canned and dry option.

Nutrient	Group A		Group B		Group C	
	Dry <sup>e</sup>	Canned <sup>f</sup>	Dry <sup>g</sup>	Canned <sup>h</sup>	Dry <sup>i</sup>	Canned <sup>j</sup>
ME (kcal/kg)*	3,942	952	3,960	1,001	3,301	941
Protein (g/100 kcal)	12.5	13.5	12.1	13.1	11.2	11.5
Fat (g/100 kcal)	5.5	4.6	5.2	4.8	4.0	4.7
Carbohydrate (g/100 kcal)	1.7	3.6	3.6	3.9	9.5	7.2
Sodium (mg/100 kcal)	94	95	98	90	100	85
EPA+DHA (mg/100 kcal)	58	21	5	80	25	111
Daidzein (µg/g) <sup>+</sup>	0 ± 0	18 ± 4	0 ± 0	10 ± 1	0 ± 0	0 ± 0
Genistein (µg/g) <sup>+</sup>	0 ± 0	19 ± 5	0 ± 0	15 ± 1	0 ± 0	0 ± 0
Main ingredients (in order by weight)	Turkey Chicken meal Chicken Herring meal Chicken fat	Water Meat by-products Chicken Wheat gluten Corn starch	Chicken BPM Corn gluten meal Pork fat Pork protein isolate Powdered cellulose	Pork by-products Pork liver Water Corn starch Cellulose	Corn Poultry BPM Corn gluten meal Animal liver flavor Animal fat	Pork by-product Water Pork liver Fish Rice

ME, metabolizable energy; BPM, by-product meal; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid \*as fed, <sup>+</sup>dry matter

analysis or stopping criteria were established before beginning the study. Data distributions were assessed with the Kolmogorov-Smirnov test. As many of the data were not normally distributed, all data are presented as median (range) and nonparametric tests were used. Baseline data among the 3 diet groups were compared by Kruskal-Wallis tests. A comparison of baseline and follow-up variables within each group was made using Wilcoxon signed ranks tests. Categorical data were compared with chi-square tests. Because this was a pilot study, *P* values were not adjusted for multiple comparisons. However, to ensure that results were consistent and biologically plausible, interpretation of the statistical analyses was considered in similar categories (eg, echocardiographic measures of left ventricular hypertrophy, liver enzymes) to help determine whether the results were likely to be spurious because approximately 40 variables were evaluated). Data were analyzed with both the intention-to-treat principle, which included all 30 cats randomized to intervention and for only the 29 cats that completed the study. Because results were similar between the intention-to-treat and per protocol analyses, only the results for the 29 cats completing the study will be presented. Statistical significance was set at *P* < .05. All statistical analyses were performed with commercially available software.<sup>k,l</sup>

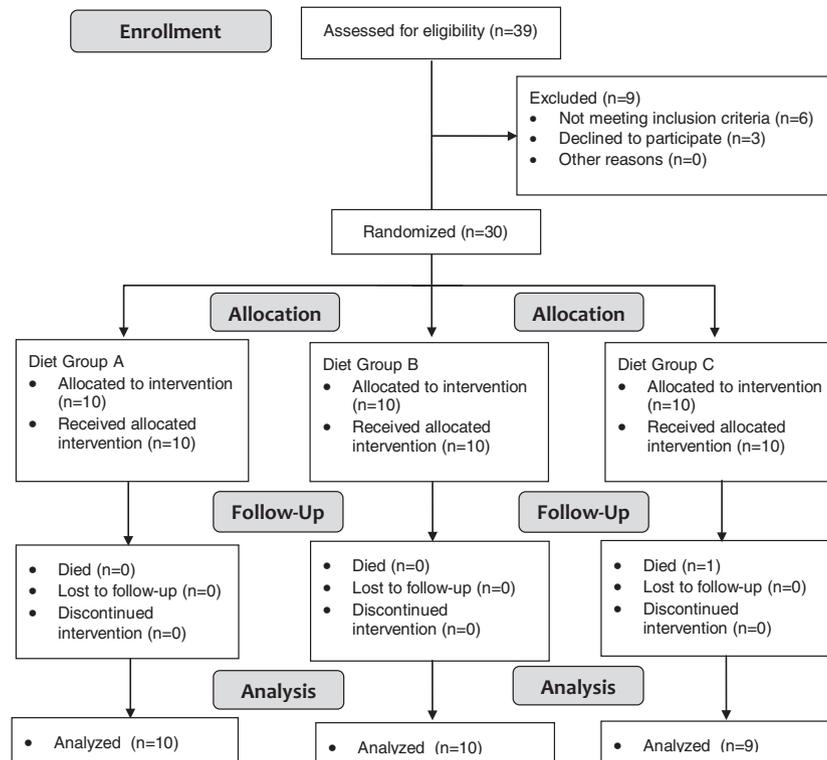
## Results

Between August 2009 and August 2012, 39 cats were screened for enrollment (Fig 1). Nine cats were excluded for reasons shown in Figure 1, and 30 cats were randomized to 1 of 3 groups. All 30 cats received the allocated intervention. Twenty-nine cats completed the 6-month study. One cat from Group C died 17 days after beginning the study because of CHF. This cat had been diagnosed with HCM and started receiving atenolol 6 months before enrollment. Subsequent data will be presented only for the 29 cats that completed the study.

There were no significant differences among the 3 diet groups at baseline in signalment (Table 2), clinical characteristics (Table 2), echocardiographic measure-

ments (Table 3), or biochemical variables (Table 4). The median age across all groups was 3.9, but ranged from 1.1 to 16.6 years. Most cats (86%) were male and all cats were neutered. All cats had been stable on any medications for at least 8 weeks. Medications included atenolol (*n* = 14; Group A [*n* = 6], Group B [*n* = 4]; Group C [*n* = 4]), clopidogrel (*n* = 4; Group A [*n* = 2], Group B [*n* = 1], Group C [*n* = 1]), and enalapril (*n* = 3; *n* = 1 in each Group). Sixteen of the 29 cats were receiving at least one of these medications, but the percentages of cats receiving at least 1 medication among the 3 groups was not significantly different (*P* = .788). Medications did not change in any cat over the course of the 6-month study.

At the time of enrollment, most cats ate all (*n* = 13; 45%) or mostly (*n* = 8; 28%) dry food, although other feeding practices included all canned (*n* = 5; 17%), 50% canned and 50% dry (*n* = 2; 7%), and mostly canned (*n* = 1; 4%). The form of food was not significantly different among groups (*P* = .158). Cats continued to eat the same forms of diet that they had eaten before starting the study (ie, if they ate all canned food before enrollment, they continued to eat all canned food during the 6-month study), with the exception of 1 cat. This cat had a history of feline idiopathic cystitis and had been eating all dry food before study enrollment. Ten weeks after enrollment, the cat had an episode of dysuria. The cat was switched to eating mostly canned food and no further episodes of dysuria occurred for the duration of the study. The median dietary sodium for all 29 cats at the time of enrollment in the study (122 mg/100 kcal [range, 82–321 mg/100 kcal]) decreased significantly after changing to the study diets (95 mg/100 kcal [range, 85–100 mg/100 kcal]; *P* < .001). There were also significant within-group decreases in dietary sodium in Diet Groups A (*P* = .021) and B (*P* = .012). However, for



**Fig 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram detailing the number of cats that were assessed for eligibility, randomized, allocated, and that completed a 6-month dietary intervention.<sup>22</sup>

**Table 2.** Baseline demographic characteristics of 29 cats with asymptomatic hypertrophic cardiomyopathy that completed a randomized study assessing 3 dietary approaches (Group A, Group B, or Group C). Baseline data for Group C represent only the 9 cats that completed the 6-month study. Data are presented as median (range).

Variable	Group A	Group B	Group C	P value
n	10	10	9	
Age (years)	4.3 (1.1–10.4)	3.9 (1.1–16.6)	4.0 (1.3–8.9)	.808
Sex				
Castrated male	9	8	8	.779
Spayed female	1	2	1	
Breed				
DSH/DLH	10	9	6	.186
Persian	0	0	1	
Peterbald	0	0	1	
Ragdoll	0	1	0	
Siamese	0	0	1	
Body weight (kg)	4.6 (3.5–6.8)	4.5 (4.1–7.2)	4.9 (4.1–6.1)	.773
Body condition score (1–9)	5 (5–7)	6 (5–9)	6 (5–8)	.512
Medications				
Atenolol	6	4	4	.645
Enalapril	1	1	1	.996
Clopidogrel	2	1	1	.779

DSH/DLH, domestic shorthair/domestic longhair.

Diet Group C, the numerical decrease in dietary sodium was not statistically significant ( $P = .066$ ).

The primary endpoints for the study were IVSd and LVWd. Neither of these primary endpoints changed significantly in any of the 3 diet groups over the course of the study (Table 3; Fig 3). One of the secondary

endpoints, left atrial dimension, decreased significantly only in Group C ( $P = .035$ ; Fig 2), while the other secondary endpoint, NT-proBNP, decreased significantly only in Group B ( $P = .013$ ; Table 4).

In addition to the primary and secondary endpoints, a number of other variables were assessed in this pilot

**Table 3.** Blood pressure and echocardiographic measurements for 29 cats with asymptomatic hypertrophic cardiomyopathy that completed a randomized study assessing 3 dietary approaches (Group A, Group B, or Group C). Baseline data for Group C represent only the 9 cats that completed the 6-month study. Data for each of the 3 groups are shown for baseline (at the time of starting the study) and at the 6-month recheck visit. Data are presented as median (range). There were no significant differences among the 3 diet groups at baseline.

Variable	Group A		Group B		Group C	
	Baseline	Recheck	Baseline	Recheck	Baseline	Recheck
BP (mmHg)	140 (103–165)	135 (105–172)	138 (118–163)	145 (115–158)	133 (101–175)	140 (102–175)
M-Mode (in cm)						
IVSd	0.65 (0.53–0.71)	0.60 (0.47–0.82)	0.67 (0.51–0.74)	0.74 (0.42–0.90)	0.68 (0.64–0.84)	0.69 (0.49–0.75)
LVIDd	1.38 (1.28–1.92)	1.49 (1.18–1.94)	1.44 (1.26–1.66)	1.38 (1.23–1.65)	1.38 (1.23–1.65)	1.43 (1.29–1.61)
LVWd	0.69 (0.56–0.98)	0.69 (0.50–1.13)	0.69 (0.50–0.94)	0.73 (0.48–0.92)	0.71 (0.51–0.92)	0.62 (0.47–0.92)
IVSs	0.87 (0.74–1.03)	0.92 (0.63–1.03)	0.90 (0.66–1.07)	0.95 (0.54–1.13)	0.89 (0.85–1.00)	0.87 (0.75–1.00)*
LVIDs	0.64 (0.30–0.96)	0.68 (0.37–0.98)	0.65 (0.45–1.00)	0.69 (0.39–0.93)	0.67 (0.41–0.89)	0.66 (0.47–0.88)
LVWs	1.00 (0.89–1.30)	0.96 (0.83–1.56)	0.92 (0.85–1.11)	1.00 (0.73–1.17)	0.98 (0.78–1.27)	0.88 (0.74–1.13)
LA	1.40 (1.15–1.96)	1.55 (1.05–2.42)	1.43 (1.24–2.10)	1.39 (1.31–2.52)	1.51 (1.18–1.61)	1.39 (1.10–1.65)*
Aorta	1.03 (0.88–1.24)	1.04 (0.86–1.19)	1.03 (0.87–1.20)	1.10 (0.80–1.35)	1.13 (0.91–1.23)	1.08 (0.95–1.24)
LA:Aorta	1.41 (0.94–1.90)	1.62 (0.96–2.03)	1.31 (1.21–2.41)	1.29 (1.15–3.15)	1.33 (1.17–1.68)	1.22 (1.02–1.70)*
2D (in cm)						
IVSd 2D	0.67 (0.51–0.95)	0.68 (0.45–0.97)	0.74 (0.51–0.89)	0.80 (0.43–0.96)	0.76 (0.70–0.95)	0.72 (0.65–0.90)
LVWd 2D	0.71 (0.50–0.96)	0.68 (0.55–1.11)	0.76 (0.56–0.90)	0.68 (0.52–1.07)	0.76 (0.59–0.92)	0.63 (0.43–1.05)
LA 2D	1.51 (1.21–2.09)	1.54 (1.37–2.31)	1.34 (1.03–2.27)	1.43 (1.05–2.51)	1.51 (1.23–1.78)	1.51 (1.10–1.63)
Aorta 2D	0.98 (0.83–1.12)	0.98 (0.79–1.09)	1.02 (0.82–1.26)	0.98 (0.73–1.16)	1.03 (0.89–1.10)	1.04 (0.85–1.21)
Doppler						
AoVEL (m/s)	1.30 (0.66–3.27)	1.05 (0.85–4.03)	2.05 (0.99–4.54)	2.04 (0.84–5.70)	1.26 (0.72–4.06)	1.45 (0.982–3.93)
E (m/s)	0.65 (0.46–0.87)	0.65 (0.53–1.12)	0.57 (0.49–0.82)	0.58 (0.05–1.19)	0.61 (0.51–0.84)	0.57 (0.48–0.85)
A (m/s)	0.84 (0.55–1.11)	0.79 (0.45–0.97)	0.78 (0.61–0.97)	0.67 (0.04–1.01)	0.77 (0.51–1.05)	0.77 (0.46–1.21)
E:A	0.78 (0.59–0.84)	0.80 (0.68–2.49)	0.78 (0.68–0.97)	0.84 (0.66–13.75)	0.84 (0.63–1.20)	0.81 (0.62–1.17)
E' LVW (m/s)	0.05 (0.03–0.08)	0.04 (0.03–0.11)	0.06 (0.03–0.07)	0.06 (0.03–0.12)	0.05 (0.02–0.09)	0.05 (0.03–0.10)
A' LVW (m/s)	0.07 (0.03–0.11)	0.05 (0.03–0.09)	0.06 (0.04–0.08)	0.05 (0.03–0.17)	0.06 (0.03–0.41)	0.05 (0.02–0.11)
E/E' LVW	13.25 (8.13–23.33)	15.50 (5.64–28.00)	10.80 (9.50–17.33)	13.17 (7.33–20.50)	11.60 (7.43–25.50)	10.40 (6.86–18.00)
IVRT (ms)	64.24 (33.27–86.26)	58.02 (34.38–98.58)	63.88 (42.50–107.80)	53.05 (42.51–80.70)	55.50 (41.90–81.30)	57.3 (41.40–94.90)

\*P < .05 comparing within group between baseline and recheck evaluations.

2D, 2-dimensional; A, late diastolic velocity of mitral inflow; A', late diastolic myocardial velocity; AoVEL, aortic velocity; AoVEL, aortic velocity; BP, blood pressure; E, early diastolic velocity of mitral inflow; E', early peak diastolic myocardial velocity; IRVT, isovolumic relaxation time; IVSd/s, interventricular septal thickness in diastole/systole; LA, left atrium; LVWd/s, left ventricular free wall thickness in diastole/systole; LVIDd/s, left ventricular internal dimension in diastole/systole.

**Table 4.** Body weight, body condition score, and laboratory measurements for 29 cats with asymptomatic hypertrophic cardiomyopathy that completed a randomized study assessing 3 dietary approaches (Group A, Group B, or Group C). Baseline data for Group C represent only the 9 cats that completed the 6-month study. Data for each of the 3 groups are shown for baseline (at the time of starting the study) and at the 6-month recheck visit. Data are presented as median (range). There were no significant differences among the 3 diet groups at baseline.

Variable	Group A		Group B		Group C	
	Baseline	Recheck	Baseline	Recheck	Baseline	Recheck
Body weight (kg)	4.6 (3.5–6.8)	4.8 (3.9–6.9)	4.5 (4.1–7.2)	4.6 (3.9–8.1)	4.9 (4.1–6.1)	4.6 (3.7–5.9)*
Body condition score (1–9)	5 (5–7)	6 (5–7)	6 (5–9)	6 (5–9)	6 (5–8)	5 (4–7)*
BUN (mg/dL)	26 (15–36)	32 (23–45)*	24 (18–33)	28 (24–43)*	27 (19–32)	27 (22–32)
Creatinine (mg/dL)	1.5 (0.9–1.9)	1.6 (0.8–1.9)	1.5 (1.2–1.7)	1.3 (0.8–1.7)*	1.3 (1.1–1.9)	1.3 (1.0–1.7)
Phosphorus (mg/dL)	4.5 (2.5–5.5)	4.5 (3.5–5.2)	4.4 (3.1–5.4)	4.3 (3.3–4.8)	4.4 (3.3–6.8)	3.8 (2.6–5.5)*
Albumin (g/dL)	3.8 (3.3–4.2)	3.9 (3.3–4.6)	3.8 (3.3–4.4)	3.8 (3.5–4.4)	3.7 (3.4–3.9)	3.8 (3.4–4.1)
ALP (U/L)	29 (17–56)	23 (13–31)	27 (12–46)	25 (13–52)	22 (12–41)	20 (10–34)*
ALT (U/L)	53 (33–219)	49 (36–71)	52 (26–81)	53 (30–66)	49 (36–67)	45 (29–60)*
AST (U/L)	29 (16–62)	27 (18–55)	32 (23–53)	29 (21–46)	27 (15–68)	22 (16–39)*
Cholesterol (mg/dL)	167 (84–262)	205 (149–259)*	173 (109–281)	235 (161–386)*	151 (105–314)	168 (108–289)
Triglycerides (mg/dL)	40 (19–112)	51 (26–106)	45 (33–117)	105 (40–709)*	44 (27–87)	40 (24–88)
Glucose (mg/dL)	107 (83–138)	104 (79–214)	100 (72–244)	94 (72–186)	109 (67–179)	110 (85–173)
Insulin (pmol/L)	100 (62–193)	75 (49–162)	114 (64–228)	145 (51–214)	119 (54–188)	106 (65–145)
HOMA	4.27 (1.83–9.12)	3.54 (1.90–5.29)	4.26 (1.64–19.76)	4.79 (1.33–10.31)	6.50 (1.76–8.27)	4.08 (1.96–5.84)
NT-proBNP (pmol/L)	535 (34–1402)	431 (24–1500)	600 (118–1158)	393 (56–1152)*	515 (24–1500)	209 (24–1500)
hs-troponin I (ng/mL)	0.31 (0.20–3.87)	0.42 (0.20–1.18)	0.47 (0.20–1.54)	0.20 (0.20–1.12)*	0.38 (0.20–0.95)	0.20 (0.20–1.25)

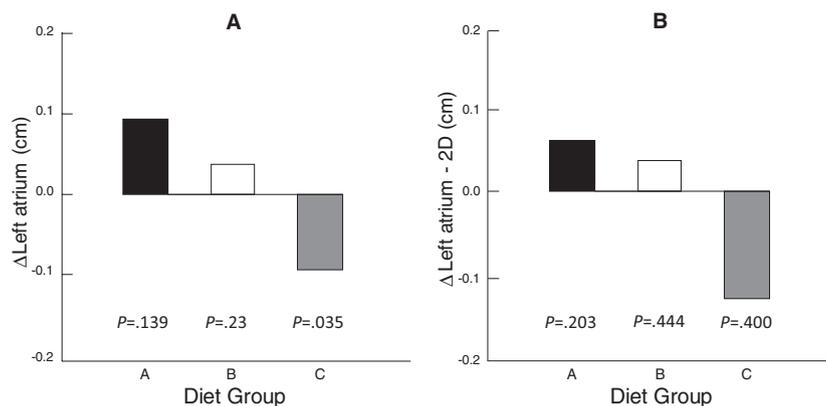
\* $P < .05$  comparing within group between baseline and recheck evaluations.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HOMA, homeostasis model assessment; NT-proBNP, N-terminal pro B-type natriuretic peptide.

study. Over the course of the 6-month study, body weight ( $P = .021$ ) and BCS ( $P = .007$ ) decreased significantly only in Group C (Table 4). Eight cats in Group C lost weight, while 6 cats in Group B and 2 cats in Group A lost weight ( $P = .01$ ). Group A had significant increases in BUN ( $P = .008$ ) and cholesterol ( $P = .021$ ). Group B had significant increases in BUN ( $P = .008$ ), cholesterol ( $P = .007$ ), and triglycerides ( $P = .005$ ), and significant decreases in NT-proBNP ( $P = .013$ ), hs-troponin I ( $P = .043$ ), and creatinine ( $P = .018$ ). Group C had significant decreases in phosphorus ( $P = .025$ ), alkaline phosphatase (ALP;  $P = .034$ ), alanine amino-

transferase (ALT;  $P = .038$ ), and aspartate aminotransferase (AST;  $P = .038$ ).

Blood pressure did not change significantly in any group (Table 3). Over the 6-month study period, in addition to the significant decrease in left atrial dimension, Group C had significant decreases in interventricular septal thickness in systole (IVSs;  $P = .038$ ; Table 3; Fig 3) and the ratio of the left atrium to the aorta ( $P = .011$ ). In Group C, there were also numerical, but not statistically significant, decreases in IVSD ( $P = .097$ ; Fig 3), LVWd ( $P = .066$ ; Fig 3), left ventricular free wall in systole (LVWs;  $P = .086$ ; Fig 3),



**Fig 2.** Median change in left atrial (M-mode; **A**) and left atrial 2D (2-dimensional; **B**) measurements for each of the 3 diet groups from baseline to 6-month recheck examination. Diet Group A (n = 10); Diet Group B (n = 10); Diet Group C (n = 9).  $P$  values are for the within-group change over the 6-month study period. Only the change for the left atrial dimension for Diet Group C was statistically significant.

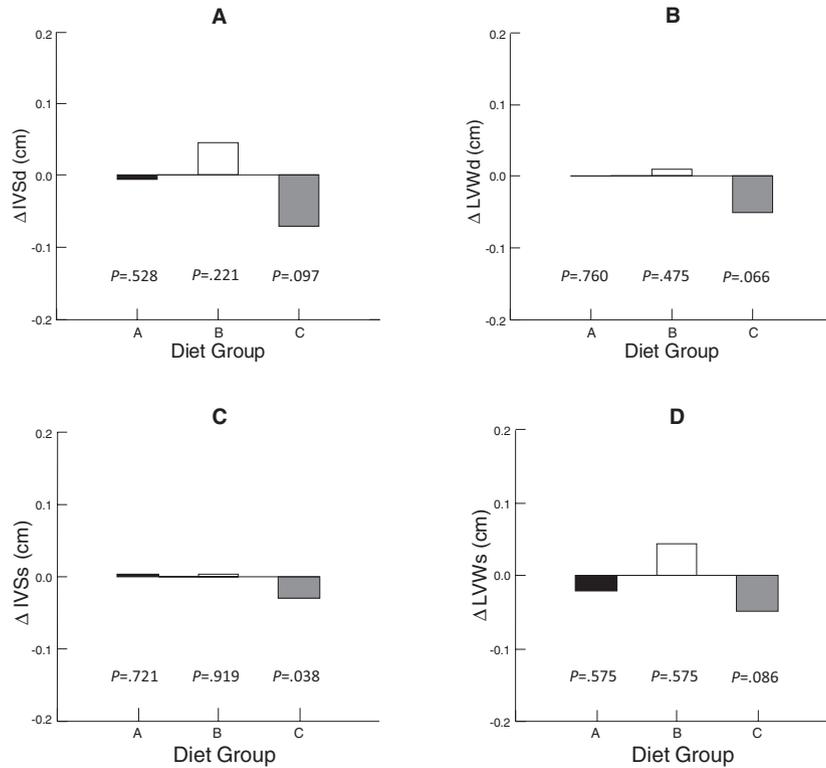
LVWd 2D ( $P = .086$ ; Fig 4), and IVSd 2D ( $P = .066$ ; Fig 4).

There were no significant differences in laboratory variables or echocardiographic measurements between cats eating all or mostly dry foods and cats eating all or mostly canned foods. There also were no significant differences in results when comparing cats

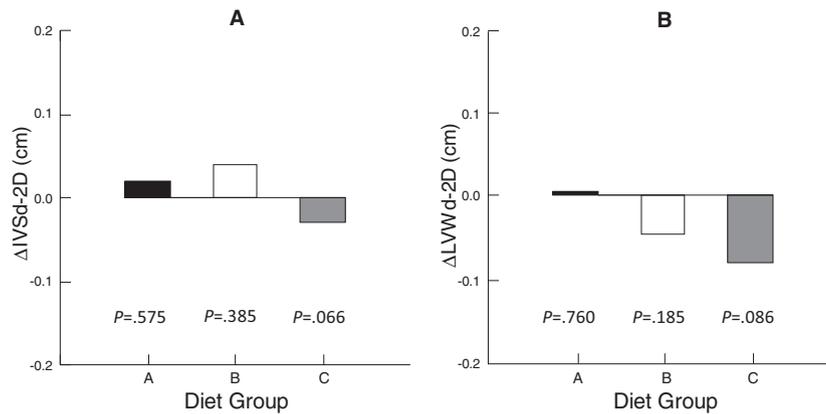
that lost weight to cats that maintained or gained weight.

### Discussion

In this small preliminary study, the 2 primary endpoints (IVSd and LVWd) did not change significantly.



**Fig 3.** Median change in interventricular septal thickness in diastole (IVSd; **A**) and systole (IVSs; **C**) and left ventricular free wall in diastole (LVWd; **B**) and systole (LVWs; **D**) for each of the 3 diet groups from baseline to 6-month recheck examination. Diet Group A (n = 10); Diet Group B (n = 10); Diet Group C (n = 9). P values are for the within-group change over the 6-month study period. Only the change for IVSs for Diet Group C was statistically significant.



**Fig 4.** Median change in 2D (2-dimensional) interventricular septal thickness in diastole (**A**) and 2D left ventricular free wall in diastole (**B**) for each of the 3 diet groups from baseline to 6-month recheck examination. Diet Group A (n = 10); Diet Group B (n = 10); Diet Group C (n = 9). P values are for the within-group change over the 6-month study period. None of the changes were statistically significant.

Left atrium (a secondary endpoint) decreased significantly over the course of the 6-month study. Interventricular septal thickness in systole, which was not a primary or secondary endpoint, also decreased significantly. However, none of the other numerical decreases in echocardiographic measures of left ventricular hypertrophy (ie, IVSd, LVWd, LVWs, IVSd 2D, LVWd 2D) were statistically significant. Although these changes are intriguing, much additional research with larger sample sizes is required to determine the true effect of diet on echocardiographic variables.

The significant decrease in NT-proBNP in Group B does not appear to be related to changes in cardiac morphology because Diet Group B did not have significant reductions in left ventricular hypertrophy. The change in NT-proBNP in Group B also might be related to variability in NT-proBNP measurements, which has been shown in dogs,<sup>14</sup> or to changes in dietary sodium intake.<sup>15</sup> Dietary sodium (on a mg/100 kcal basis) decreased significantly for all 29 cats as a group, and individually for Diet Groups A and B. The current study did not measure absolute food intake, which would have allowed for calculation of sodium intake on a mg/day basis and is a limitation, but the fact that the median sodium content of the diet decreased significantly suggests that cats were likely to also have a decrease in their total daily sodium intake. This emphasizes the importance of obtaining a complete diet history for cats with cardiac disease at every visit.<sup>7</sup> High-sensitivity troponin I also decreased significantly only in Diet Group B, but possible relationships between diet and hs-troponin I are not well documented.

Because some metabolic changes have been seen in previous studies of cats with HCM<sup>16,17</sup> and because the macronutrient properties of the test diets could result in biochemical changes, a number of additional variables were evaluated in this study. Groups A and B showed a significant increase in BUN, without a concomitant increase in creatinine. While an increased BUN:creatinine ratio can occur for a number of reasons (eg, GI bleeding, pre- or postrenal azotemia, catabolism), the finding in the current study was most likely related to the relatively high protein content of these 2 diets (12.1–13.5 g/100 kcal). Although the protein content of the diets used in Group C (11.2–11.5 g/100 kcal) was slightly lower than the protein of the diets in Groups A and B, it is still well above the Association of American Feed Control Officials Cat Food Nutrient Profile minimum of 6.5 g/100 kcal for adult maintenance. The effect of changes in BUN or creatinine on myocardial hypertrophy or on the progression of HCM is unknown. Cholesterol (for Group A) and triglycerides (for Groups A and B) increased significantly during the 6-month study, but did not change in Group C. This is probably related to the dietary fat content, which was lower in Group C, but also might be influenced by the fact that some of the cats in Group C lost weight over the course of study. Cholesterol and triglyceride concentrations were not significantly different in a study of Maine Coon cats with and without HCM,<sup>17</sup> so the effect of changes in

cholesterol and triglycerides in HCM is unknown. It is unclear why ALP, ALT, AST activities all decreased significantly in Group C. This might be related to effects of lower dietary fat content,<sup>18</sup> weight loss,<sup>19</sup> or, for the ALT and AST (for which there are myocardial isoenzymes), reduced myocardial injury.<sup>20</sup>

As a result of the dietary properties selected for the test diets used in the current study, the calorie density of the diets fed in Group C (particularly the dry option, the most commonly eaten form) was lower than in the diets fed in Groups A and B. Accordingly, the median body weight and body condition score in Group C decreased significantly, and 8 of the 9 cats in this group lost body weight. The goal of the study was to have all cats maintain body weight during the study, so owners were instructed to feed an amount to maintain current body weight for the duration of the study. Owners also were encouraged to weigh the cat during the study, especially if body weight appeared to be changing so that adjustment of food amounts could be made. Nonetheless, the lower calorie density (and insufficient frequency of weighing) probably resulted in weight loss in Group C. While statistical analysis did not show a difference in echocardiographic or biochemical variables between cats that lost weight and those that maintained or gained weight, it cannot be excluded that the weight loss itself, rather than the diet, resulted in changes. One case report showed significant echocardiographic improvements in a 17-year-old boy with HCM after weight loss (from 137.9 to 88.9 kg).<sup>21</sup> Research on possible direct effects of weight loss on echocardiographic and laboratory parameters is warranted.

In addition to the important limitation of weight loss in Group C, this study had a number of other limitations that must be addressed. As previously mentioned, commercially available foods with specific properties were selected, rather than formulating specific experimental diets for this pilot study. While the foods selected had the specific properties the investigators desired to test, some of the carbohydrate, fat, and ingredient differences were not as distinct as could be achieved with experimental diets, and nutrients other than the ones being tested also were different (eg, vitamins, minerals). In addition, while canned and dry versions within each group were selected to be as similar as possible, there were some differences, both in profile and in ingredients, between the 2 forms of food. While most cats (69%) ate all or mostly dry food, these differences between the canned and dry forms inevitably resulted in additional variation in nutrient intake within each group.

Another limitation is the small sample size of this study. Because previous studies were not available to confirm the investigators' hypothesis that diet could modify these variables, the study was designed to confirm or refute this hypothesis before embarking on a larger, more expensive study. Therefore, statistical power was insufficient to identify statistical differences for many of the endpoints, if there was indeed a difference. Another issue that might have affected results is the duration of the treatment (ie, 6 months). Longer

studies are probably needed to see full effects of dietary modification on echocardiographic variables. Given the changes that were seen in the current study, both those that were significant and the other consistent trends, the investigators believe that further studies based on what has been learned from this study are warranted.

Other limitations of the study include medications and disease severity. Cats were not prohibited from receiving medications in the current study as long as they had been receiving the medication for at least 8 weeks and, in fact, 55% of cats in the study were receiving at least 1 cardiac medication. Although there were no differences in medications among the 3 groups, there is potential for effects of medication on echocardiographic variables. In addition, while all cats were categorized as ISACHC Stage 1b at the beginning of the study, the severity of disease varied (eg, degree of left ventricular hypertrophy, left atrial enlargement, left ventricular outflow tract obstruction). Future studies should control for both of these factors to address their potential effects on endpoints.

Finally, it must be acknowledged that changes in echocardiographic parameters (ie, reduction in left atrial size or degree of left ventricular hypertrophy) do not necessarily equate to a better outcome, slower progression, or longer survival, and additional studies are required to prove that even if dietary modification can result in improved echocardiographic changes, that this translates to improved clinical outcome.

Nonetheless, the results of this study suggest that diet might modify some biochemical and echocardiographic variables in cats with HCM without clinical signs. Additional studies are needed to determine the effects of nutrition on phenotypic expression of cardiac disease.

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### Footnotes

<sup>a</sup> GE Vivid 7 Dimension, General Electric Healthcare, Milwaukee, WI

<sup>b</sup> Human Insulin Specific Immunoassay, Millipore, St Charles, MO

<sup>c</sup> Immulite 2000<sup>®</sup> Immunoassay System, Siemens Medical Solutions, Inc., Malvern, PA

<sup>d</sup> Feline CardioPet NT-proBNP, IDEXX Laboratories, Westbrook, ME

<sup>e</sup> EVO<sup>®</sup> Turkey & Chicken Formula Dry Cat & Kitten Food, Natura Pet Products, Fremont, NE

<sup>f</sup> Pro Plan<sup>®</sup> Urinary Tract Health Formula Chicken Entree - In Gravy, Nestlé Purina PetCare, St Louis, MO

<sup>g</sup> Prescription Diet<sup>®</sup> m/d<sup>®</sup> Feline dry, Hill's Pet Nutrition, Topeka, KS

<sup>h</sup> Prescription Diet<sup>®</sup> m/d<sup>®</sup> Feline canned, Hill's Pet Nutrition

<sup>i</sup> Purina Veterinary Diets<sup>®</sup> DH Dental Health Formula, Nestlé Purina PetCare

<sup>j</sup> Prescription Diet<sup>®</sup> c/d<sup>®</sup> Multicare with Seafood Feline canned, Hill's Pet Nutrition

<sup>k</sup> SPSS 21.0, SPSS, Chicago, IL

<sup>l</sup> Systat 13.0, Systat Software, Chicago, IL

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