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Isolated discrete upper septal thickening in a non-referral cat population of senior and young cats

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KEYWORDS
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Abstract *Introduction/objectives:* Discrete upper septal thickening (DUST) is a phenotype of elderly people. The cardiac phenotype in senior cats has been incompletely described. We aimed to characterize the echocardiographic phenotype of senior cats, specifically to determine prevalence of DUST and hypertrophic cardiomyopathy (HCM).
Animals: One hundred and forty-nine healthy, normotensive cats.
Materials and methods: Prospective cross-sectional study. Senior (≥9 years) and young (<6 years) cats were recruited from non-referral population. We defined DUST as an isolated basilar septal bulge, and HCM as left ventricular wall thickness ≥6 mm. An interventricular septum ratio (basal-to-mid septal thickness ratio) was calculated. We assessed for associations between clinical and echocardiographic variables and DUST. Data are presented as mean (±SD), median (range), or frequency (percentage).
Results: One-hundred and two senior and 47 young cats were enrolled. Aortoseptal angle (AoSA) was steeper in senior cats (137° (±14.5) vs. 145° (±12.3) in young cats, P=0.002). Eighteen cats had DUST (18/149, 12%), fourteen senior, and four young cats (P=0.4). Cats with DUST had steeper AoSA (125° (±8.3) vs. 142° (±13.7), P<0.0001) and higher interventricular septum ratio (1.4 (1.2—2.0) vs. 1.0 (0.7—1.8)). Univariable analysis showed decreased odds of DUST with greater AoSA (OR 0.9, P<0.0001), age was not associated with DUST. Twenty-nine senior cats had HCM (28.4%).

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Discussion/conclusions: Prevalence of DUST was 12%. There was no association between age and DUST. Smaller/steeper AoSA was the main factor associated with DUST. There was a high prevalence of HCM in this senior population.

Abbreviations

95% CI	confidence interval
AoSA	aortoseptal angle
DUST	discrete upper septal thickening
HCM	hypertrophic cardiomyopathy
IVS	interventricular septum
IVS ratio	basal-to-mid septal thickness ratio
LA/Ao	left atrium to aorta ratio
LAD	left atrial diameter
LV	left ventricular
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
LVWT	left ventricular wall thickness
RPLA	right parasternal long-axis view
RPSA	right parasternal short-axis view
SAM	systolic anterior motion of the mitral valve
SHT	systemic hypertension

Introduction

The cardiac phenotype in healthy senior cats has been incompletely described in the veterinary literature. A study assessing tissue Doppler imaging in senior cats with different systemic diseases identified a high percentage of cats with an isolated basilar septal bulge [1]. An isolated bulge in the basilar septum, i.e. a focal septal thickening, has been extensively described in the human literature [2—11], but only in a scarce number of reports in the veterinary literature [1,12—14].[c] Multiple terms have been used to describe this localized/isolated septal bulge in people, such as discrete upper septal thickening (DUST) [3,4], ventricular septal bulge [5,6,9], sigmoid septum [15—17], isolated basal septal hypertrophy [8,17,18], discrete upper septal hypertrophy [11], or isolated septal thickening [19]. The veterinary literature has also used various terms to describe this finding, DUST,[c] isolated basal septal hypertrophy [14], basilar septal bulge [1], or sub-aortic focal interventricular septal hypertrophy [13]. In humans, a basilar septal bulge has been considered a phenotype of the elderly [2—4,6—8,16—18] and the same has been suggested in cats [1,14].

Hypertrophic cardiomyopathy (HCM) has an age-related penetrance in both humans and cats [20,21], and thus, a higher prevalence of HCM in senior individuals is expected. A large study in a general, non-referral population of apparently healthy cats showed that 29.4% of cats over 9 years of age had HCM vs. 14.3% in cats under three years of age [21].

The present study aimed to characterize the two-dimensional echocardiographic cardiac phenotype of apparently healthy senior cats in a large non-referral population. Specifically, we aimed to determine the proportion of elderly cats with DUST and to assess the prevalence of HCM.

Animals, materials, and methods

This study was approved by the Clinical Research Ethical Review Board of the Royal Veterinary College (URN 2015-1378). This was a prospective cross-sectional study. Apparently healthy senior (age 9 years or above) and young cats (under 6 years old) from non-referral populations were recruited. The latter was used as a control group. Senior cats were recruited from two first opinion practices in London (People's Dispensary for Sick Animals in Bow and Beaumont Sainsbury Animal Hospital in Camden) and from two rehoming centers in the UK (Battersea Dogs & Cats Home's and Cats Protection's National Cat Center). Young cats were client-owned pet cats being screened for blood donation at the Queen Mother Hospital for Animals (Royal Veterinary College). All cats were deemed healthy if they did not have any clinical signs of systemic or cardiac disease, had a normal physical examination and normal blood work, including complete blood count, biochemistry, T4 (only measured in senior cats), and negative FeLV/FIV snap test and FeLV provirus test (only systematically measured in young cats). Cats with

[c] Singletary G, Oyama MA. Survival of cats with isolated discrete upper septal thickening (DUST) vs. cats with and without cardiomyopathy. Research Comunications of the 2012 ACVIM Forum, New Orleans, Louisiana. Abstract C-47 May—June 2012.

hyperthyroidism were excluded. Systemic blood pressure was measured in senior cats and cats with systolic blood pressure >160 mmHg were excluded. Cats with a heart murmur and/or arrhythmia were not excluded if they were asymptomatic.

Senior cats recruited at the first opinion practices were part of a large diet study (control healthy group). One observer (JNM) visited the practices once a week over a period of 12 months and scanned all cats that were part of the diet trial. The senior cats recruited from rehoming centers were part of a large longitudinal study assessing the natural history of HCM in a non-referral population (the CatScan II study) [22]. The young cat group was cats being screened for suitability for becoming a blood donor, all potential blood donors in our hospital have an echocardiogram performed as part of their initial assessment. Feline blood donors are recruited at the Queen Mother Hospital for Animals through leaflets and advertisements on social media. Blood donors can be between one and 10 years old, but for the present study, only cats under 6 years were included. All cats screened as part of the blood donation program during the study period were included regardless of whether they proved to be suitable for recruitment as a blood donor after echocardiography (i.e. cats with heart disease were not excluded from the study).

Echocardiographic data

Echocardiograms were performed using an ultrasound machine[d] with a 7.5 or 12 MHz phased-array transducer by a board-certified veterinary cardiologist (JNM) or a cardiology resident under direct supervision of a board-certified cardiologist. One observer (JNM) reviewed and remeasured all echocardiographic examinations prior to data analysis. The observer was not blinded to the study groups, while the data were being reviewed, remeasured, and analyzed.

General variables

Left ventricular (LV) wall thickness (LVWT) was measured from two-dimensional images: a right parasternal long-axis view (RPLA) and a right parasternal short-axis view (RPSA) at the papillary muscle level. Three LV segments were measured in each view, as previously described [23]. In brief, the basal segment and mid segment of the interventricular septum (IVS) in RPLA, left and right segment of the IVS in RPSA, and LV free wall in both RPSA and RPLA [23]. These were measured using a leading edge to leading edge technique and averaged over three cardiac cycles. The overall thickest segment from all the measurements was used for the LVWT. All LVWT measurements were performed at end-diastole, defined as the first frame after mitral valve closure in a RPLA and as the greatest LV internal diameter in a RPSA. Cardiac chambers were measured in two-dimensional images by an inner edge to inner edge technique at the interface between the blood pool and myocardial wall. Left ventricular internal diameter in diastole was measured from a RPLA and a RPSA at the level of the chordae tendineae, in an end-diastolic frame, on three different cardiac cycles in each view. The averaged LV internal diameter on these two views was recorded, and the highest value was used for data analysis.

Left atrial dimension was measured by both the ratio of the left atrium-to-aorta (LA/Ao) and the left atrial diameter (LAD). The LA/Ao was measured from a RPSA at the heart base, in the frame after aortic valve closure (end-ventricular systole) [24], and LAD was measured as the maximal cranial-caudal LA dimension from a RPLA four-chamber view, in the frame before mitral valve opening (end-ventricular systole) [25].

Left atrial and LV fractional shortening were measured by M-Mode from a RPSA at the heart base and at the papillary muscle, respectively [24]. The presence of systolic anterior motion of the mitral valve (SAM) was assessed on two-dimensional and color Doppler echocardiography from a RPLA five-chamber view, as a systolic motion of the tip of the anterior mitral valve leaflet toward the IVS with turbulent flow in the LV outflow tract (LVOT).

Aortoseptal angle

The aortoseptal angle (AoSA) was defined as the angle between the mid-line axis of the ascending aorta and that of the IVS, as previously described [26—28]. The AoSA was determined in a RPLA five-chamber view at end-diastole (first frame after mitral valve closure) in three different cardiac cycles, as follows. Three still RPLA five-chamber images from each cat (447 images in total) were imported into a graphics software,[e] and in each image, the aorta and IVS mid-line axes were defined, respectively, by drawing two lines at the

[d] GE Systems, Hatfield, Hertfordshire, UK.

[e] PowerPoint, Microsoft Office, version 16.3 (2019), Cambridge, UK.

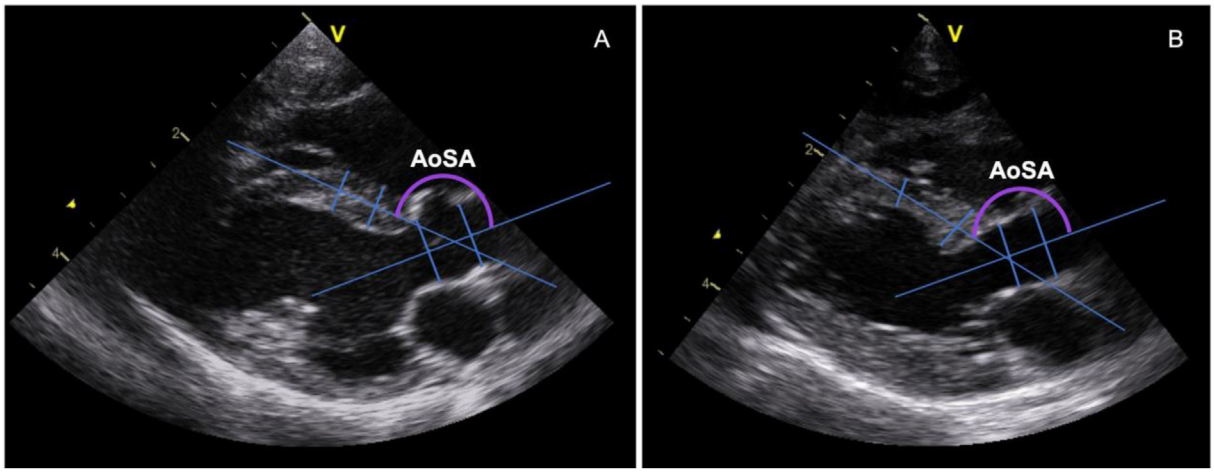

Fig. 1 Aortoseptal angle (AoSA) measurement in two different cats. (**A**) Cat without a discrete upper septal thickening (No-DUST); (**B**) cat with an isolated discrete upper septal thickening (DUST).

aortic annulus and sinotubular junction and two transverse lines at approximately the first- and mid-third of the IVS. The mid-points of each of these lines were used to draw a line that defined the aorta and IVS axis. Finally, the AoSA was measured as the angle where the two lines defining the mid-line axes crossed (Fig. 1); this was performed using an open-source image processing software.[f] The averaged AoSA of the three images in each cat was used for data analysis.

Interventricular septum ratio

The maximum basal and mid IVS segments wall thickness was measured in the RPLA five-chamber view at end-diastole, and a basal-to-mid septal thickness ratio (IVS ratio) calculated, as basal-IVSd divided by mid-IVSd (basal-IVSd/mid-IVSd) [3,10].

Discrete upper septal thickening

Discrete upper septal thickening was defined as an isolated bulge in the first-third segment (most basilar) of the IVS. No specific septal wall thickness cut-off was used to define DUST, but rather, a visual assessment was performed. Discrete upper septal thickening was diagnosed based on the presence of an isolated basilar septal bulge, i.e. a 'dune-like' structure protruding into the LVOT [6] without any other LV segment thickening (Fig. 2). Thus, for DUST to be present, LV thickening was only allowed at the basilar septum and all other LV segments had to be $<$5.5 mm. Moreover, wall motion in the mid-IVS had to be normal, as infarcts/fibrosis at the mid-IVS may result in a basilar bulge [3].

Hypertrophic cardiomyopathy and other cardiomyopathies

Hypertrophic cardiomyopathy was defined as LVWT $\geq$6 mm, in the absence of hyperthyroidism or systemic hypertension (SHT, systolic blood pressure $>$160 mmHg), which were both study exclusion criteria. Equivocal for HCM was defined as LVWT 5.5—5.9 mm, and restrictive cardiomyopathy was defined as LVWT $<$5.5 mm with left atrial enlargement (LA/Ao $>$1.6) [29].

Clinical data

Data collated at the time of echocardiographic examination included body weight, body condition score (BCS), age, sex, breed, and presence of a murmur, gallop, or arrhythmia. Systolic blood pressure was measured in senior cats using a Doppler device according to the American College of Veterinary Internal Medicine consensus statement [30].

Statistical analysis

Data were tested for normality graphically and by a Shapiro—Wilk test. Normally distributed data are reported as mean (±standard deviation) and non-normally distributed data as median (range). Categorical data are presented as frequency and percentage (95% confidence intervals, 95% CI). Comparisons between groups (senior cats vs. young cats or DUST vs. No DUST) for continuous variables

[f] Fiji, version 2.0.0-rc-67/1.52c.

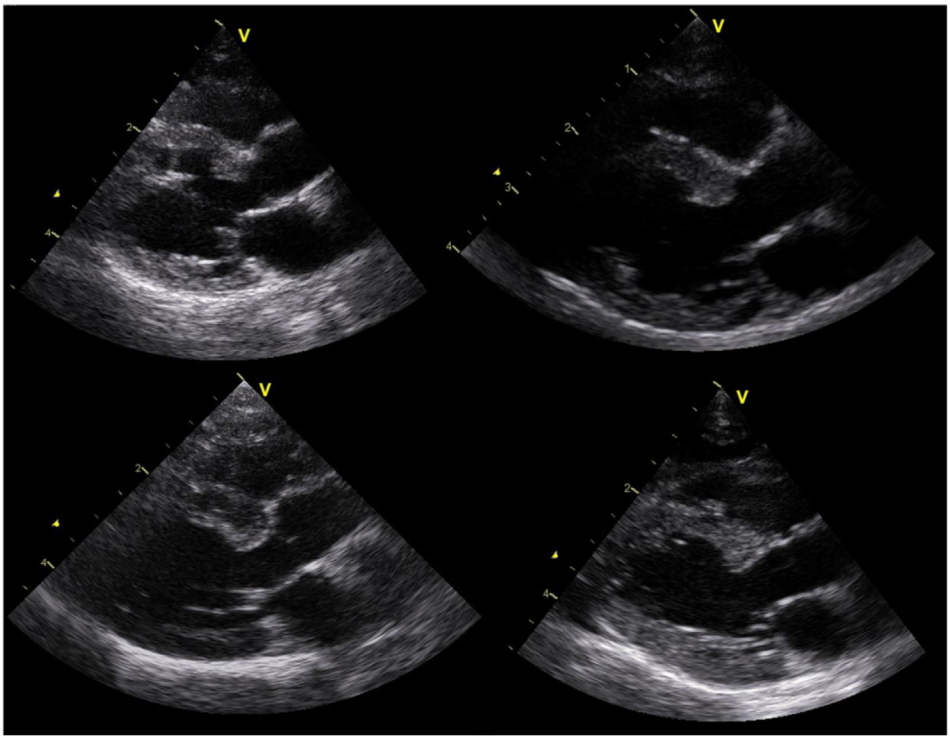

Fig. 2 Discrete upper septal thickening (DUST) in four different cats. Discrete upper septal thickening was defined as an isolated basilar septal bulge protruding into the left ventricular outflow tract.

were carried out by Mann—Whitney U-test or Students' independent *t*-test for non-normally or normally distributed data, respectively. Categorical variables were compared between-groups by Fisher's exact.

Spearman correlation analyses were performed to assess the association of basal-IVSd thickness with AoSA and blood pressure.

Univariable binary logistic regression was performed to identify factors associated with DUST (coded as No DUST = 0, DUST = 1). The following clinical and echocardiographic variables were considered: study group (young cats = 0, senior cats = 1), systolic blood pressure (continuous), left atrial size (LA/Ao and LAD, continuous), and AoSA (continuous). Odds ratios and 95% CI were calculated.

There are scarce data in the literature on prevalence of DUST in cats, which limits sample size calculations. In two studies, DUST was described in 2/8 (25%) cats and 17/66 (25.8%) cats over 9 years old and 1/62 (1.6%) cat under 6 years old [1,12]. Based on these data, sample size calculation for testing two independent proportions (P1 = 0.25 and P2 = 0.016) suggested that we would need to recruit 40 cats to each study group (senior cat group and young cat group) by using a continuity correction (ratio (r) = 1, $\alpha = 0.05$, $\beta = 0.20$).

P values <0.05 were considered statistically significant. Statistical analysis was performed by commercially available software.[g,h]

Results

One hundred and 53 cats were evaluated with 4/153 cats excluded from the final data analyses: one cat had pleural and pericardial effusions, while three cats had poor echocardiographic image quality and RPLA five-chamber views were not available. Seven senior cats had mild azotemia (creatinine 161 (155—213) μmol/L, reference <153 μmol/L), but they were not excluded as they had not clinical signs related to kidney disease. Thus, data from 149 cats were assessed, comprising 102 senior cats and 47 young cats. In the senior cat group, median age was 12.5 (9—18.2) years with 88/102 (86.3%) cats ≥10 years old, and in the young cat group, median age was 2.6 (0.9—5.2) years.

The majority of enrolled cats (135/149, 90.6%) were non-pedigree. There were five Maine Coon cats, two British shorthair, two Ocicat, two

[g] SPSS 25-26, 2018—2019.
[h] GraphPad Prism 7, 2016.

Siamese, one British Blue, one Russian Blue, and one Norwegian Forest cat. Pedigree cats were over-represented in the young cat group (21% of young cats were pedigree vs. 4% of senior cats, P=0.002). There were 90/149 (60%) male cats in the whole population, with no difference in sex proportion between groups. Likewise, body weight was similar between groups. Senior cats had a higher prevalence of heart murmurs (57% vs. 16%, P=0.0002) and a higher heart rate (P=0.04). Blood pressure was not available in any of the young cats but mean systolic blood pressure was 131 (±17) mmHg in the senior group. Summary of the main clinical characteristics of the studied population is described in Table 1.

Echocardiographic data

Senior cats had thicker LVWT than young cats (5.2 (3.1–9.2) mm vs. 4.7 (3.7–5.8) mm, respectively, P=0.0004). Left atrial size was not different between groups (LA/Ao, P=0.2; LAD, P=0.3), but senior cats had lower left atrial fractional shortening (27% (6–38) vs. 29% (19–39), P=0.009). Left ventricular fractional shortening was similar between groups (P=0.6). The AoSA was smaller (steeper) in senior cats (137° (±14.6) vs. 145° (±12.3), P=0.002) (Fig. 3). The prevalence of DUST in our population was 12.1% (95% CI 7.8–18.3%). The proportion of DUST was not different between the two age groups (14/102, 13.7% (95% CI 8.4–21.7%) cats in the senior group and 4/47, 8.5% (95% CI 3.4–19.9%) cats in the young group, P=0.4). A summary of the general echocardiographic variables assessed in this study is described in Table 2.

Discrete upper septal thickening

A summary of selected clinical and echocardiographic variables in cats with DUST is described in Table 3. There were no significant differences between cats with and without DUST in terms of prevalence of heart murmurs, sex, or blood pressure. Cats with DUST had smaller (steeper) AoSA (125° (±8.3) vs. 142° (±13.7) in No-DUST cats, P<0.0001) (Figs. 3 and 4) and a higher IVS ratio (median IVS ratio 1.4 in DUST vs. 1.0 in No-DUST cats) (Fig. 5). None of the cats with DUST had SAM. Four cats with DUST had a basilar IVSd wall thickness ≥6 mm. There was no correlation between basal-IVSd thickness and AoSA (P=0.1) or blood pressure (P=0.4).

In univariable analysis, the only factor associated with DUST was a smaller (steeper) AoSA (Table 4). A greater (less steep) AoSA was associated with decreased odds of DUST (odds ratio 0.9, 95% CI 0.85–0.94, P<0.0001).

Hypertrophic cardiomyopathy

There were no cats with HCM in the young cat group. The prevalence of HCM in the 102 senior cats was 28.4% (95% CI 21–38%). Eleven HCM cats had SAM (11/29, 38%). Cats with HCM were 12.3 (±1.9) years old and 22/29 (76%) were male. They had a LVWT of 6.5 (5.4–9.2) mm and most had normal left atrial size, LAD 16.2 (±2.3) mm and LA/Ao 1.4 (1.0–2.5), with a median left atrial fractional shortening of 24% (6–33). One cat had a LVWT of 5.4 mm and LV fractional shortening of 29% and was classified as end-stage HCM, as previous echocardiograms had showed LVWT >6 mm. Aortoseptal angle was 140° (±14.4°) in cats with HCM, and there was no difference in AoSA between those cats with SAM, 138° (±18.1), and those without SAM, 140° (±12.0), p=0.7.

There were 13/149 (9%) cats equivocal for HCM (LVWT 5.7 [5.5–5.9] mm), 3/13 cats in the young cat group and 10/16 cats from the senior cat group. Three cats (3/149, 2%) in the senior group had a restrictive cardiomyopathy phenotype (LVWT between 4.1 and 5.2 mm and LA/Ao 1.7–1.8).

Table 1 Clinical characteristics of senior and young cats.

	All cats	Senior	Young	P value
N	149	102	47	
Age (years)	10.8 [0.9–18.2]	12.5 [9–18.2]	2.6 [0.9–5.2]	
Breed				
Pedigree (%)	14 (9.4)	4 (3.9)	**10 (21)**	***0.002***
Male (%)	90 (60)	60 (59)	30 (64)	*0.7*
Weight (kg) (n = 121)	4.5 (±1.1)	4.5 (±1.1)	4.7 (±0.9)	*0.4*
Murmur (%) (n = 126)	62 (49%)	**58 (57%)**	4 (16%)	***0.0002***
Heart rate (n = 107)	180 [128–260]	**180** [128–260]	160 [140–200]	***0.04***

Continuous variables are reported as mean (±standard deviation) or median [range], and categorical variables are reported as frequency (N) and percentage (%). Statistically significant differences (P<0.05) are highlighted in bold.
N: number of cats.

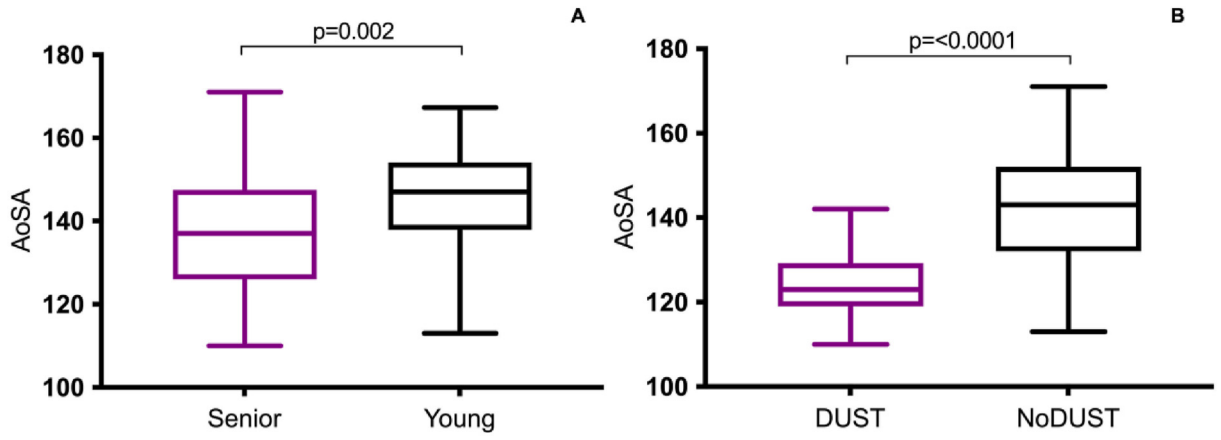

Fig. 3 Box (25th percentile, median, and 75th percentile) and whiskers (minimum to maximum) plots comparing aortoseptal angle (AoSA) in senior and young cats (**A**) and in cats with and without discrete upper septal thickening (DUST) (**B**).

Table 2 Echocardiographic variables in senior and young cats.

	All cats	Senior	Young	P value
N	149	102	47	
LVWT (mm)	5 [3.1—9.2]	**5.2 (3.1—9.2)**	4.7 (3.7—5.8)	***0.0004***
IVSd (mm)	4.9 [2.6—7.8]	**5.1 (±1.0)**	4.6 (±0.6)	***0.001***
LVFWd (mm)	4.5 [3.0—9.2]	**4.7 (3.0—9.2)**	4.5 (3.5—5.3)	***0.03***
LVIDd (mm)	15.2 (±1.9)	15.1 (±1.9)	15.5 (±1.9)	*0.2*
LAD (mm) (n = 146)	15.1 (±1.9)	15.2 (±2.0)	14.8 (±1.6)	*0.3*
LA/Ao (n = 148)	1.4 (±0.2)	1.4 (±0.2)	1.3 (±0.1)	*0.2*
LAFS% (n = 146)	28 (6—39]	**27 (6—38)**	29 (19—39)	***0.009***
LVFS% (n = 113)	46 (±7.7)	46 (±7.4)	45 (±8.1)	*0.6*
DUST (n (%))	18 (12.1)	14 (13.7)	4 (8.5)	*0.4*
AoSA (n = 147)	141° (110—171)	**137° (±14.6)**	145° (±12.3)	***0.002***

Continuous variables are reported as mean (±standard deviation) or median [range], and categorical variables are reported as frequency (n) and percentage (%). Statistically significant differences (P<0.05) are highlighted in bold.
AoSA: aortoseptal angle; DUST: discrete upper septal thickening; IVSd: interventricular septal thickness at end-diastole; LAD: left atrial diameter; LA/Ao: left atrium to aorta ratio; LAFS%: left atrial fractional shortening; LVIDd: left ventricular internal diameter at end-diastole; LVFWd: left ventricular free wall thickness at end-diastole; LVFS%: left ventricular fractional shortening; LVWT: maximal left ventricular wall thickness; N: number of cat.

Table 3 Clinical and echocardiographic variables in cats with and without a discrete upper septal thickening.

	All cats	DUST	No DUST	P value
N	149	18	131	
Age (years)	10.8 (0.9—18.2)	11.8 (1.7—18)	10.6 (0.9—18.2)	*0.2*
Murmur (%) (n = 126)	62 (49)	6 (37.5)	56 (51)	*0.4*
Male (%)	90 (60)	11 (61)	79 (60)	*1.0*
Blood pressure (n = 93)	131 (±17)	145 (100—157)	130 (93—160)	*0.2*
Base-IVSd (mm)	4.5 [2.5—7.6]	**5.2 (3.6—6.5)**	4.4 (2.5—7.6)	***0.0008***
Mid-IVSd (mm)	4.4 [2.6—7.1]	**3.8 (2.6—5.0)**	4.5 (2.9—7.1)	***0.0001***
IVS ratio (n = 148)	1 [0.7—2]	**1.4 (1.2—2.0)**	1 (0.7—1.8)	—
AoSA angle (n = 147)	141° [110—171]	**125° (±8.3)**	142° (±13.7)	***<0.0001***

Continuous variables are reported as mean (±standard deviation) or median [range], and categorical variables are reported as frequency (N) and percentage (%). Statistically significant differences (P<0.05) are highlighted in bold.
AoSA: aortoseptal angle; DUST: discrete upper septal thickening; IVSd: interventricular septal thickness at end-diastole; IVS ratio: base-IVSd/mid-IVSd; LAD: left atrial diameter; N: number of cats.

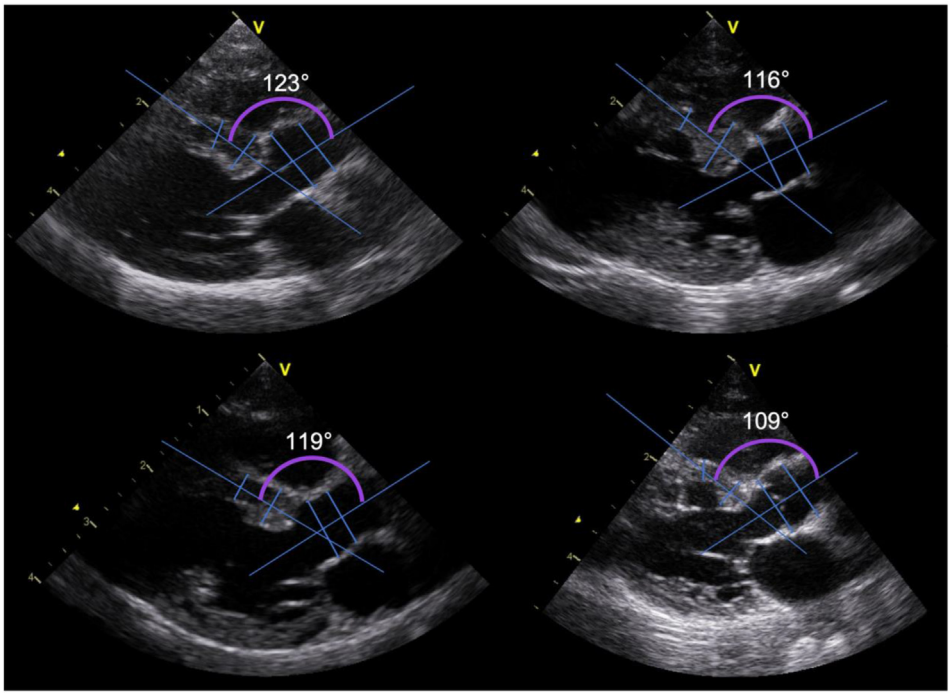

Fig. 4 Aortoseptal angle (AoSA) in four cats with discrete upper septal thickening (DUST). Cats with discrete upper septal thickening had smaller (steeper) AoSA.

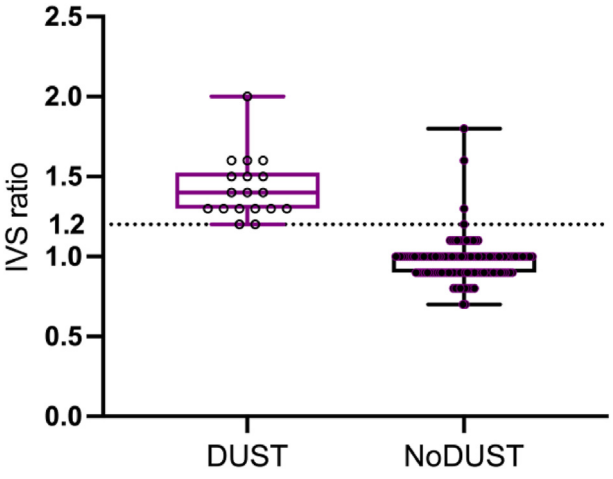

Fig. 5 Box (25th percentile, median, and 75th percentile) and whiskers (minimum to maximum) plots with individual data points depicting interventricular septum (IVS) ratio (basal-to-mid septal thickness ratio) in cats with and without discrete upper septal thickening (DUST). All cats with DUST had an IVS ratio $\geq$1.2. The four cats without DUST with IVS ratio $\geq$1.2 were cats with HCM and left ventricular hypertrophy affecting more than one ventricular segment.

Table 4 Univariable logistic regression assessing factors associated with discrete upper septal thickening.

	Odds ratio	95% CI	P value
Study group			
Young cats	Reference		
Senior cats	1.7	0.5—5.5	0.4
Blood pressure	1.0	1.0—1.1	0.3
AoSA	**0.9**	**0.85—0.94**	**<0.0001**
LA/Ao	0.1	0.007—2.2	0.2
LAD	0.9	0.7—1.2	0.4

Statistically significant differences (P<0.05) are highlighted in bold.
AoSA: aortoseptal angle; CI: confidence interval; LAD: left atrial diameter; LA/Ao: left atrium to aorta ratio.

Discussion

In this cross-sectional study, we evaluated an apparently healthy, non-referral cat population of senior and young cats with echocardiography. We focused on the presence of DUST and HCM in these two distinct age groups, aiming to characterize the cardiac phenotype of senior cats. The main findings were as follows: (1) DUST was observed in 12% of cats; (2) there was no difference in the proportion of DUST between senior and young cats; (2) senior cats had significantly smaller (steeper) AoSA than young cats; (3) cats with DUST had smaller (steeper) AoSA; (4) the prevalence of HCM in the senior group was 28.4%, and none of the young cats had HCM.

The diagnostic criteria for DUST have not been clearly established either in the human [17,31] or the veterinary literature. Multiple criteria have been used in people to define DUST [31]. Depending on the study, these have included one or more of the following: (1) visual assessment, where DUST is defined as an isolated thickening in the first-third of the IVS (basal segment of the IVS), i.e. a dune-like structure bulging in the LVOT [2–7,15]; (2) basilar IVS thickness >12–15 mm [3,4,6,8,11]; (3) basal to mid-IVS thickness ratio >1.3–1.5, basilar IVS LVWT >50% than mid-IVS or basilar IVS with LVWT ≥2 mm than mid-IVS [3,6,9–11]; (4) the absence of wall motion abnormalities in the mid-septum that could be consistent with myocardial infarction [3–5].

There are scarce data on DUST in the veterinary literature, and the only criterion reported to date has been isolated basal IVS hypertrophy ≥6 mm [1,12–14,28]. Considering the limited studies on DUST in cats, the controversy about LVWT cut-offs to define HCM in cats [32] and the recognized challenge of differentiation between HCM and DUST in humans [2,5,7,11,31,33], we chose to define DUST in our study based on visual assessment of an isolated IVS basilar bulge, avoiding use of a potentially controversial LVWT cut-off.

We calculated an IVS ratio (basal-to-mid septal thickness ratio) in all cats in the study, as this has been frequently used in people to diagnose DUST [3,6,9–11]. All cats with DUST, as defined in the present study, had an IVS ratio ≥1.2 (1.2–2.0). There were only four cats without DUST that had IVS ratio ≥1.2, but these were cats with HCM and LV hypertrophy in more than one LV segment (HCM cats with LV hypertrophy in the septum plus LV free wall) (Fig. 5). Thus, based on our results, IVS ratio might be useful to define DUST in cats.

Reports vary widely on the prevalence of DUST in people, ranging from 0.5% to 44% [3,6–10,18,19]. This might reflect different definitions of DUST between studies [18] and also different study populations (non-referral/community vs. referral).

We observed DUST in 12% (18/149) of the studied cats. If we had used a stricter criterion to define DUST, such as a basilar IVS wall thickness ≥6 mm, the prevalence would have been 3% (4/149 cats). This is similar to the prevalence previously described in a non-referral cat population (3/103 cats, 3%) [12] but lower than the reported prevalence in a mixed population of referral and first-opinion cases (17/66 senior cats, 26%) [1], and in a referral cat population (20/122 cats, 16%) [14]. It has been suggested that the prevalence of DUST increases with age in humans [2–4,6–8,16,18] and in one study in cats [14]. In the present study, there was no difference in the proportion of cats with DUST in senior vs. young cats.

In people, DUST is considered to mainly affect the elderly and debate over whether it is a physiologic or pathologic phenomenon [18].

Discrete upper septal thickening has been frequently associated with SHT [3,10,11,18,19,34]. It has been suggested that the basilar septum is more prone to hypertrophy than other LV segments [18]. The basilar septum may operate at an increased load (wall stress), as its longitudinal fibers have larger radii that other LV segments of the heart, which can expose them to increased wall tension according to Laplace's law [35], also as the basilar septum is the last ventricular segment to be electrically activated, earlier contractions of other LV segments during systole may augment its wall stress, and lastly, the right ventricle also causes additional pressure on the septum [18]. Thus, increased afterload in a LV segment that is already exposed to higher wall stress, may cause it to thicken earlier than the neighboring segments, and this might be the reasoning for DUST in people with early SHT [10,18,19,34]. Therefore, DUST has then been considered a specific pattern of LV hypertrophy in SHT [3,19,34]. In cats, one study has suggested that SHT might be associated with DUST [36], but in another study where DUST was identified in a large proportion of senior cats (17/66 cats), all had normal blood pressure [1].

In humans, DUST has also been suggested to be present in prehypertensive individuals [10]. Prehypertension has been recently described in veterinary medicine as values of systolic blood pressure ranging between 140 and 159 mmHg [30]. We had 33 cats with blood pressure between 140 and 160 mmHg, but DUST was not more prevalent in this group of cats (DUST was present in 8/33 cats with blood pressure 140–160 mmHg vs. 6/60 cats with blood pressure <140 mmHg, $p=0.08$).

Nevertheless, a large study in healthy human adults did not show an association between DUST and systolic blood pressure or SHT in multivariable analysis [6]. Considering the high prevalence of both DUST and SHT in senior patients, it has been suggested that these might be co-existing entities rather than cause and effect [8].

Discrete upper septal thickening has been associated with a smaller AoSA in humans [2,5,9,15–17,26,31]. It has been suggested that the aortic dilation and lengthening associated with age may push the IVS downward and kink its basilar segment, causing a smaller AoSA and DUST [9]. A smaller AoSA might also be associated with changes

in blood flow pattern (non-laminar flow) across the LVOT, increasing shear stress at the basilar septum and subsequently causing focal hypertrophy [5]. This hypothesis has also been suggested as a mechanism involved in triggering subaortic stenosis in both humans [37] and dogs [27], as changes in blood flow caused by a smaller AoSA could increase shear stress in the LVOT and contribute to the subvalvular lesion through stimulation of growth factors and cellular proliferation [37].

In the present study, we only evaluated normotensive cats and thus DUST was not secondary to SHT. However, a smaller AoSA is a plausible trigger of DUST in our study. Both cats with DUST and senior cats had a smaller AoSA. Although senior cats in our study did not have a higher prevalence of DUST than young cats, they did have a significantly smaller AoSA and this was associated with increased odds of DUST. Thus, it seems that DUST may be observed in young cats if they have a small AoSA, and based on our data, this could be one of the main factors triggering DUST.

An association between LV outflow tract obstruction (LVOTO) and DUST has been suggested [8], but in a study evaluating individuals with DUST with and without LVOTO, there was no difference in basilar septal thickness or AoSA. There were differences in LV hypercontractility and mitral valve apparatus morphology [8], factors known to be critical in causing LVOTO in HCM [38]. Thus, DUST *per se* does not seem to be associated with LVOTO [8]. We did not have data on LVOT velocity in this cohort of cats, so we could not evaluate the association between DUST and LVOT gradient, but as none of the cats with DUST had SAM, it seems less likely that DUST in our population was causing LVOTO.

In humans, HCM patients have been suggested to have a smaller AoSA than controls and HCM patients with smaller AoSA had higher LVOT gradients and provokable LVOTO [39,40]. This was not however observed in a feline HCM study [28], nor did we find a difference in AoSA between HCM cats with and without SAM in the present study.

It is challenging to differentiate HCM from DUST, as there is an overlap in the echocardiographic features of these two entities [2,5,7,8,11,31,33]. Some proposed distinctive features of DUST in humans include the absence of familial history, gender preference, or ECG changes [8]. The presence of LVOTO has been used as a criterion to differentiate these two conditions [7,31]. Also, individuals with DUST have generally less severe hypertrophy and by definition normal LVWT in all LV segments besides the basilar septum [31]. Moreover, HCM cases have been suggested to have more severe diastolic dysfunction [11].

The classic histopathological features of HCM, namely myocyte hypertrophy, fibrosis, and myocyte disarray [41], have not been assessed in DUST populations [31], although the absence of myofiber disarray in a DUST patient was described in one study [7], and disarray was documented less frequently in septal myectomy specimens of elderly HCM patients compared with young HCM patients [42].

In the present study, 4/18 cats with DUST met the criteria for both HCM (LVWT $\geq$6 mm) and DUST (isolated IVS bulge), thus reiterating the overlap between these entities diagnostic features.

Limitations

Our study has several limitations. An important limitation is that our study groups are from two different sources, thus representing two different populations. This might have affected our analyses. These samples were only defined based on age categories, and we cannot exclude that the samples differed in other unmeasured variables, which could have affected the prevalence of DUST. Moreover, our cohorts were cats taking part on longitudinal studies (senior cat group) and a blood donor program (young cat group), and there might have been selection biases on these cohorts, as several factors might affect owners' decisions in enrolling their cats in such studies/programs.

An experienced single observer assessed and measured all echocardiograms with the aim of minimizing operator variability, although intra-operator repeatability on AoSA and qualitative assessment of DUST was not analyzed. Moreover, and most importantly, the observer was not blinded to the study groups, and this is especially relevant as we defined DUST by visual assessment. Thus, biases on the assessment of DUST might have been introduced.

Blood pressure was not measured in the young cat group. We cannot, therefore, exclude SHT as a cause of DUST in the young cats. But it is unlikely that healthy young cats had SHT.

Our definition of senior cats was arbitrary. Recent guidelines suggested defining senior cats as $>$10 years old [43]. We defined senior cats as $\geq$ 9 years old, as this is an age group where there is an increased risk of hyperthyroidism and SHT, which are important HCM phenocopies [30,44,45]. Thus, we wanted to assess the echocardiographic cardiac phenotype in this age group. Nevertheless, 86.3% of the cats enrolled in our study were $\geq$10 years

old, thus our study population did not deviate markedly from the current definition of senior cats [43].

This was a cross-sectional study, so it was not possible to assess prognosis associated with DUST.

In people, DUST has been frequently suggested to be associated with SHT [3,4,10,11,18,19,34]. In this study, SHT was an exclusion criterion, so we were unable to assess the association between SHT and DUST.

Conclusions

Discrete upper septal thickening was observed in 12% of the studied cats. Although the prevalence of DUST was not significantly different between senior and young cats, a small AoSA appeared to be the main factor associated with DUST in this population of healthy, normotensive cats. We also documented a high prevalence of HCM in a general, apparently healthy population of senior cats.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

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