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Left atrial size and volume in cats with primary cardiomyopathy with and without congestive heart failure☆

L. Duler, DVM, K.F. Scollan, DVM*, N.L. LeBlanc, DVM, MS

Department of Clinical Sciences, Carlson College of Veterinary Medicine, Oregon State University, Corvallis, OR, 97331, USA

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Abstract *Introduction/objectives:* Myocardial diseases are the most common acquired cardiac diseases in cats and may result in left atrial enlargement and congestive heart failure (CHF). Volume calculations have replaced linear measurements for chamber quantification in humans but are not commonly measured in cats. The aims of this retrospective study were to compare the left atrial (LA) size by two-dimensional linear measurements to two-dimensional LA volumes (LAV).
Animals: One hundred sixty-two client-owned cats were included.
Materials and methods: Cats with complete echocardiographic examinations were included and categorized into one of the three groups: healthy, cardiomyopathy (CM), and CHF. Seven measurements of the LA size were performed including minimal and maximal LA-to-aortic ratio (LA:Ao) and LAV and also maximal left atrial diameter (LAD).
Results: Cats were classified as healthy (n = 56), CM (n = 62), and CHF (n = 44). The minimal LA:Ao (LA:Ao_{min}) and minimal LAV from the left apical view ($LAV_{min\text{-}LAP}$) best differentiated the CM and CHF groups. The LA:Ao_{min} value with the optimal sensitivity and specificity to distinguish CM and CHF cats was 1.64 (sensitivity 84% and specificity 75%).
Conclusions: Left atrial volumes were not superior to linear measurements of LA size in distinguishing CM and CHF cats in this study. Minimal LA size and volumes resulted in a larger area under the curve than each corresponding maximal value.

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* Corresponding author.
E-mail address: kate.scollan@oregonstate.edu (K.F. Scollan).

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Minimum LA size may be a better prognostic factor of CHF in cats with CM.
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Abbreviations

AUC	area under the curve
CHF	congestive heart failure
CM	cardiomyopathy(ies)
DCM	dilated cardiomyopathy
H	healthy
HCM	hypertrophic cardiomyopathy
LA	left atrium/left atrial
$LA:Ao_{max}$	maximal left atrial-to-aortic ratio; start of ventricular diastole following aortic valve closure
$LA:Ao_{min}$	minimal left atrial-to-aortic ratio; end of ventricular diastole following ECG P wave
LAD	left atrial diameter; end of ventricular systole, last frame before mitral valve opening
LAE	left atrial enlargement
LAP	left apical
LAV	left atrial volume
LAV_{max}	maximal left atrial volume; end of ventricular systole, last frame before mitral valve opening
LAV_{min}	minimal left atrial volume; end of ventricular diastole following ECG P wave
LV	left ventricle/ventricular
MOD	method of discs
RPLA	right parasternal long axis
RCM	restrictive cardiomyopathy
ROC	receiver operator characteristic
UCM	unclassified cardiomyopathy

Introduction

Cardiomyopathies (CMs) are the most common acquired feline cardiac diseases and include idiopathic hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), and unclassified cardiomyopathy (UCM) [1—6]. In addition, cats can develop secondary CM due to systemic diseases which may resolve with appropriate therapy of the underlying condition but can progress to congestive heart failure (CHF) if the underlying etiology is untreated or progressive [7]. Overall, primary myocardial disease underlies the majority of feline CHF cases presented to veterinary centers [5,8].

Primary myocardial diseases are characterized by progressive diastolic dysfunction in both cats [9,10] and humans [11]. Diastolic dysfunction can be assessed by a number of echocardiographic variables, including assessment of left atrial (LA) size, mitral inflow spectral Doppler patterns, tissue Doppler imaging, and speckle tracking echocardiography [10,12]. As a result of ventricular diastolic dysfunction, left-sided CHF may occur. Congestive heart failure is one of the most common and deleterious clinical sequelae in cats with primary CM diseases [13] and is characterized by pulmonary edema, pleural effusion, or both [14,15]. Left atrial enlargement (LAE) may precede the development of left-sided CHF. While dogs generally have identifiable radiographic LAE in cases of CHF, cats may lack radiographic LAE in some cases of CHF, making echocardiographic assessment of LA size critically important [16].

The LA may enlarge in various directions, although is conventionally measured echocardiographically in cats using a linear measurement from a two-dimensional still image from the right parasternal short-axis view, which is indexed to the aortic root diameter (i.e. left atrium-to-aortic root ratio, LA:Ao). This measurement is performed at early ventricular diastole following closure of the aortic valve leaflets and prior to opening of the mitral valve leaflets, when the LA should be at its maximal size during ventricular diastole [17,18]. The maximal left atrial diameter (LAD), measured at end ventricular systole just prior to the mitral valve leaflets opening from a right parasternal long-axis view (RPLA), has also been utilized as an assessment of LA size [19]. Two-dimensional measurements and volume calculations have replaced one-dimensional linear measurements for chamber quantification in humans [20,21] and are increasingly reported in dogs [22,23]. Left atrial volumes (LAVs) in cats have been reported in a limited number of veterinary studies [24] but are not routinely measured during echocardiographic examinations of cats with or without cardiac disease. Few studies have assessed minimal values of LA size in cats [24,25], although they have been reported in humans to have a better correlation

with diastolic dysfunction [26] and left ventricular (LV) filling pressure [27].

The objectives of this retrospective study were to compare LA size quantification using linear and two-dimensional variables in cats with and without CHF due to primary CM disease. A secondary aim was to compare measurements of minimal versus maximal LA size to discriminate between cats with and without CHF. We hypothesized that LAV would better differentiate cats with and without CHF due to primary CM disease than linear measurements. Secondly, we hypothesized that minimum measures of LA size would better differentiate CHF from non-CHF cats than maximum values.

Animals, materials and methods

Animals

Medical records were searched to identify feline patients that had a complete echocardiographic examination performed at the Oregon State University Veterinary Teaching Hospital between January 2008 and July 2017 and had a diagnosis of primary CM (HCM, RCM, UCM, or DCM) with or without left-sided CHF, as well as cats which were echocardiographically normal. Cats were excluded if they were diagnosed with systemic hypertension or hyperthyroidism or if these diseases had not been excluded in cats diagnosed with CM that were greater than 8 years of age. Cats were included if they were diagnosed with hyperthyroidism with evidence of a normalized T4 value for more than 3 months prior to the echocardiogram [28]. Cats were also excluded if their ECG was consistent with sustained ventricular tachycardia, accelerated idioventricular rhythm, or atrial fibrillation. Information regarding sedation given at referral practices was inconsistently present in the medical records; therefore, cats were not excluded if sedation was used. Cats suspected of right-sided CHF based on severe right atrial or biatrial enlargement with ascites, pericardial effusion, or pleural effusion were excluded. A diagnosis of left-sided CHF was established by clinical history, radiographic evidence of pulmonary venous distension, pulmonary edema, radiographic or echocardiographic evidence of pleural effusion, or both, and response to heart failure treatment. Patients with incomplete echocardiographic studies or studies with poor image quality were excluded. If a patient presented several times through the study period, only the first echocardiogram was included for review.

Cats were categorized into three groups: (1) the healthy control group (H) with normal echocardiographic findings, (2) cardiomyopathy group (CM) with echocardiographic diagnosis of HCM, RCM, DCM, or UCM but without clinical or radiographic evidence of left-sided CHF, and (3) left-sided CHF group (CHF group) with echocardiographic CM and clinical or radiographic evidence of CHF. Data collected from the medical record included the date of presentation, breed, sex, neuter status, weight, age, cardiac medications, cardiac diagnosis, and evidence of CHF.

Echocardiographic variables

Cats were diagnosed with primary CM by echocardiography at the time of evaluation. To diagnose HCM, the end-diastolic LV free wall or interventricular septal thickness was greater or equal to 6 mm until September 2016 or greater than weight-based 95% prediction intervals after September 2016 [29]. Restrictive cardiomyopathy was diagnosed when LAE was found with a non-dilated LV with normal wall thicknesses, with or without systolic dysfunction. Dilated cardiomyopathy was diagnosed if the LV or both ventricles were dilated with reduced systolic function. A diagnosis of UCM was made when the cardiomyopathic changes did not fit into a previously described category.

All echocardiograms were performed by a board-certified cardiologist or a cardiology resident under the supervision of a cardiologist with a simultaneous ECG tracing and stored off-line on one of the three commercially available ultrasound software packages [a, b, c]. Echocardiographic measurements were performed on 3 representative, but not always consecutive, cardiac cycles and averaged. The LAV measurements were recorded as raw volumes (mL) and also indexed to body weight and recorded as mL/kg.

The echocardiographic measurements for this study were performed by a small animal specialty intern (L.D.) and reviewed by a board-certified cardiologist (K.F.S.). Seven measurements of LA size were performed on each study (Fig. 1). The LA:Ao was measured from the right parasternal short-axis view as described by Hansson et al. [17] at two time points in the cardiac cycle. The maximal LA:Ao (1, Fig. 1A; $LA:Ao_{max}$) was measured at the beginning of ventricular diastole, directly

[a] EchoPac, GE Healthcare, Wauwatosa, WI, USA.
[b] Xcelera, Philips Medical Systems, Andover, MA, USA.
[c] TOMTEC Imaging Systems GmbH, Munich, Germany.

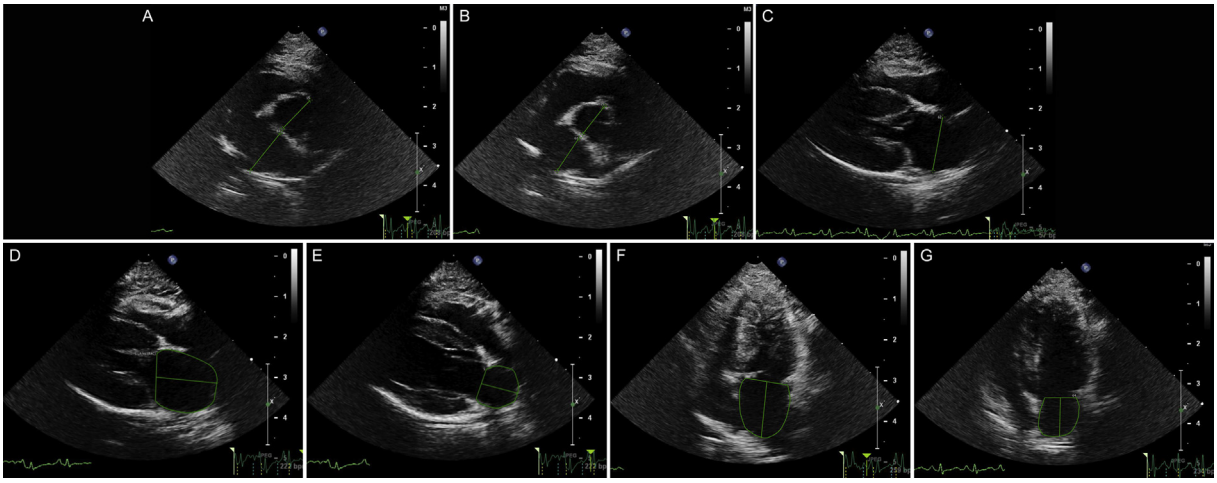

Fig. 1 Echocardiographic measurements of left atrial size and volume from the right parasternal short-axis view (A, B), right parasternal long-axis view (C, D, E), and left apical view (F, G). Maximal left atrial-to-aortic ratio (LA:Ao) was measured directly following closure of the aortic valve leaflets in early ventricular diastole (A). Left atrial diameter (LAD) was measured parallel to the mitral valve annulus at the widest point on the frame prior to mitral valve opening at end ventricular systole (C). Maximal left atrial volumes (LAVs) were measured on the frame prior to mitral valve opening at end ventricular systole (D, F). Minimum values of the LA:Ao and LAV were measured directly after the P wave on the ECG tracing at end ventricular diastole (B, E, G). Left atrial volumes were made by tracing the endocardial border and calculated using the monoplane Simpson's method of discs.

following closure of the aortic valve leaflets, and the minimal LA:Ao (2, Fig. 1B; $LA:Ao_{min}$) was measured just after the P wave on the ECG tracing. The maximal and minimal LAV was measured using the monoplane modified Simpson's method of discs (MOD) from the RPLA 4-chamber view (3, Fig. 1D; $LAV_{max\text{-}RPLA}$ and 4, Fig. 1E; $LAV_{min\text{-}RPLA}$) and the left apical (LAP) 4-chamber view (5, Fig. 1F; $LAV_{max\text{-}LAP}$ and 6, Fig. 1G; $LAV_{min\text{-}LAP}$) [20]. Maximal LAV measurements were made on the frame prior to mitral valve opening, and the minimal measurements were made just following the ECG P wave. Lastly, the maximal LAD from the RPLA 4-chamber view (7, Fig. 1C) was measured at the end of ventricular systole at the last frame before mitral valve opening [24]. For the RPLA and LAP views, special care was taken to use only images that did not include the aorta or LV outflow tract for the LAV and LAD measurements.

Statistical analyses were performed with a commercially available software[d]. Normality of data was assessed with the D'Agostino & Pearson normality test. Normally distributed data were reported as mean ± standard deviation, while non-normally distributed data were reported as median and interquartile range. Variables were compared between groups using the Kruskal–Wallis test with Dunn's correction for multiple comparisons. Views (RPLA versus LAP) were compared for the entire study population using the Wilcoxon matched-pairs signed-rank test. Receiver operator characteristic (ROC) curves were used to assess the area under the curve (AUC), sensitivity, specificity, and optimal cutoff values to distinguish groups. A P value of <0.05 was considered significant.

Results

Initial medical records review yielded 111 healthy cats with a normal echocardiogram and 254 cats with an echocardiographic diagnosis of CM. Cats were excluded for the following reasons: incomplete echocardiographic study or poor image quality (n = 71), elevated thyroid hormone or inability to exclude hyperthyroidism in patients older than 8 years and suspected of HCM (n = 42), diagnosis equivocal for CM (n = 39), evidence of right-sided CHF (n = 22), suspicion of systemic hypertension or inability to exclude systemic hypertension in a patient aged > 8 years and suspected of HCM (n = 10), incomplete medical record (n = 9), primary valvular disease (n = 8), third-degree atrioventricular block (n = 1), and hyperaldosteronism due to an adrenal tumor (n = 1).

A total of 162 cats were subsequently included in the study: 56 in the H group, 62 in the CM group,

[d] GraphPad Prism, version 7.0c, GraphPad Software, Inc., La Jolla, CA, USA.

Table 1 Demographic data and medications administered prior to echocardiography for the 162 cats.

Variable	H (n = 56)	CM (n = 62)	CHF (n = 44)
Age (years)	3 (1.25–5.75)	9 (5–12)	10 (5.25–12.8)
Sex			
Number of male (intact/neutered)	27 (14/13)	38 (2/36)	28 (0/28)
Number of female (intact/spayed)	29 (17/12)	24 (0/24)	16 (0/16)
Body weight (kg)	4.4 (3.5–5.4)	4.7 (3.8–5.6)	4.4 (3.5–5.6)
Breeds			
American shorthair	1	–	–
Abyssinian	–	1	–
Bengal	16	2	–
Birman	1	–	1
Burmese	–	–	1
Domestic medium hair	1	5	3
Domestic Longhair	2	3	3
Domestic shorthair	13	35	26
Himalayan	–	1	–
Maine coon	7	5	2
Manx	–	2	–
Norwegian forest cat	–	1	–
Persian	–	1	1
Ragdoll	–	1	1
Savannah	–	1	–
Siamese	2	3	4
Siberian	11	–	–
Sphynx	2	1	–
Tonkinese	–	–	2
Type of cardiomyopathy			
HCM	–	45	14
RCM	–	4	14
UCM	–	12	14
DCM	–	1	2
Cardiac medications			
Intravenous or oral furosemide	–	9	28
Oral benazepril	–	2	3
Oral atenolol	–	2	1
Oral pimobendan	–	0	1

Data are presented as median and interquartile range.
CHF, congestive heart failure; CM, cardiomyopathy; DCM, dilated cardiomyopathy; H, healthy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; UCM, unclassified cardiomyopathy.

and 44 in the CHF group. Ninety-three of the patients (57%) were male (16 intact and 77 neutered) and 69 (43%) were female (17 intact and 52 spayed). The demographic data of the three groups, including median age and weight, are presented in Table 1. Cats in the H group were younger than the cats in both the CM and CHF groups ($p < 0.0001$), and the three groups did not statistically differ in body weight. The most common breed was Domestic shorthair (n = 74; 46%), followed by Bengal (n = 18; 11%) and Maine coon (n = 14; 9%). Cats in the H group presented most commonly for cardiac screening (n = 28), breeding soundness examination (n = 9), or murmur evaluation (n = 5). Three cats presented for evaluation of each of the following: gallop rhythm, ECG abnormality, dyspnea, and suspected radiographic cardiomegaly. One cat was evaluated for coughing and one for exercise intolerance.

Of the 106 cats diagnosed with CM, 59 were diagnosed with HCM (56%), 26 with UCM (24%), 18 with RCM (17%), and 3 with DCM (3%). Forty-three cats (40%) were receiving at least one cardiac medication at the time of the diagnosis. Among the CHF cats, 32 (73%) presented with pulmonary edema alone, 6 (14%) with pulmonary edema and pleural effusion, 4 (9%) with pleural effusion alone, 1 cat with pulmonary edema and pericardial effusion, and 1 with pericardial and pleural effusion. Two cats, both in the CM group, were previously diagnosed with an elevated T4 value and had been documented to have euthyroid for 4

Table 2 Echocardiographic measurements from healthy (H), primary cardiomyopathy (CM), and congestive heart failure (CHF) cats.

Variable	H	CM	CHF
$LA:Ao_{min}$	1.12 (0.99–1.23)	1.22 (1.07–1.71)	2.2 (1.75–2.45)
$LA:Ao_{max}$	1.47 (1.37–1.67)	1.66 (1.38–1.92)	2.38 (1.98–2.57)
LAD (cm)	1.5 (1.32–1.68)	1.66 (1.39–1.87)	1.93 (1.62–2.13)
$LAV_{min\text{-}RPLA}$ (mL)	0.61 (0.48–0.80)	1.1 (0.59–1.98)	3.5 (2.26–4.69)
$LAV_{max\text{-}RPLA}$ (mL)	1.95 (1.37–2.71)	2.35 (1.78–4.38)	4.95 (3.34–6.01)
$LAV_{min\text{-}LAP}$ (mL)	0.53 (0.41–0.80)	0.83 (0.56–1.55)	2.72 (1.37–4.28)
$LAV_{max\text{-}LAP}$ (mL)	1.77 (1.42–2.28)	2.36 (1.56–3.62)	3.87 (2.45–6.13)
$LAV_{min\text{-}RPLA}$ (mL/kg)	0.15 (0.11–0.21)	0.21 (0.14–0.48)	0.69 (0.45–0.88)
$LAV_{max\text{-}RPLA}$ (mL/kg)	0.46 (0.32–0.63)	0.54 (0.39–0.90)	0.94 (0.60–1.3)
$LAV_{min\text{-}LAP}$ (mL/kg)	0.13 (0.10–0.19)	0.18 (0.13–0.35)	0.54 (0.33–0.98)
$LAV_{max\text{-}LAP}$ (m/kgL)	0.43 (0.34–0.50)	0.49 (0.34–0.81)	0.84 (0.60–1.2)

Data are presented as median and interquartile range.
$LA:Ao_{min}$, minimal left atrial-to-aortic ratio, measured at end-diastole just after the P wave; $LA:Ao_{max}$, maximal left atrial-to-aortic ratio, measured at early diastole at aortic valve closure; LAD, left atrial diameter measured at end-systole just prior to mitral valve opening; $LAV_{min\text{-}LAP}$, minimal left atrial volume from the left apical view measured at end-diastole just after the P wave; $LAV_{max\text{-}LAP}$, maximal left atrial volume from the left apical view measured at end-systole just prior to mitral valve opening; $LAV_{min\text{-}RPLA}$, minimal left atrial volume from the right parasternal long-axis view measured at end-diastole just after the P wave; $LAV_{max\text{-}RPLA}$, maximal left atrial volume from the right parasternal long-axis view measured at end-systole just prior to mitral valve opening.

months and 3 years, respectively, prior to evaluation.

There were 9 cats in the CM group that were given furosemide by either their primary care veterinarian or an emergency clinic for suspected CHF prior to presentation for cardiac evaluation. In each case, the furosemide was discontinued following their cardiac evaluation after exclusion of CHF. Of these cats, 8 of 9 cats received between 1 and 3 doses of 1–2 mg/kg within 24 h prior to presentation. One cat received a single subcutaneous dose of 4.7 mg/kg two days prior to echocardiographic imaging.

Of the 44 cats included in the CHF group, 43 of 44 had active CHF at the time of the echocardiogram. One cat had been treated with furosemide (3.2 mg/kg/day) for 10 days prior to evaluation and recheck chest x-rays showed resolution of the previous CHF at the time of the echocardiogram. Of cats with active CHF at the time of their echocardiogram, 42 of 43 cats were evaluated at their first episode of CHF and one cat had been treated for CHF for the preceding 11 months with daily oral furosemide (1.6 mg/kg/day). Of the cats that presented for their first episode of CHF, 16 of 42 had not received any diuretic prior to their echocardiogram, while 26 had received varying amounts of furosemide in the preceding 24 h. For 24 of 26 cats, the mean dose of furosemide given was 3.3 ± 1.6 mg/kg within the preceding 24-h period, and for two cats, the dose of furosemide given was not recorded in the medical record.

The results of the LA size and volume measurements are presented in Table 2 (raw and indexed data) and Figure 2 (raw data). Measurements of each variable were statistically different between all three groups with the exception of $LAV_{max\text{-}LAP}$ and LAD. The $LAV_{max\text{-}LAP}$ measurement was not statistically different between the H and CM groups, while the LAD measurement was only significantly different between the H and CHF groups. Left atrial volume measurements for all cats obtained from the RPLA (0.96 mL, 0.58–2.4 mL) and LAP (0.92 mL, 0.48–1.9 mL) views were statistically different ($p = 0.0005$).

Based on the ROC analysis (Table 3 and Fig. 3), $LA:Ao_{min}$ (AUC = 0.839), indexed $LAV_{min\text{-}LAP}$ (AUC = 0.828), and $LAV_{min\text{-}LAP}$ (AUC = 0.824) resulted in the largest AUCs to distinguish CM from CHF cats. Indexing LAV to body weight slightly increased the AUC for both $LAV_{min\text{-}LAP}$ and $LAV_{max\text{-}LAP}$ and slightly decreased it for the RPLA LAV measurements (Table 3). All seven measurements had poor AUC results to distinguish H and CM cats (data not shown). The $LA:Ao_{min}$ value with the optimal sensitivity and specificity to distinguish CM and CHF cats was 1.64 (sensitivity 84% and specificity 75%). The $LAV_{min\text{-}LAP}$ raw and indexed values with optimal sensitivity and specificity to distinguish CM and CHF cats were 1.46 mL (sensitivity 73% and specificity 75%) and 0.3 mL/kg (sensitivity 81% and specificity 73%), respectively.

An additional ROC subanalysis was performed to assess the AUC to distinguish CM cats with LAE

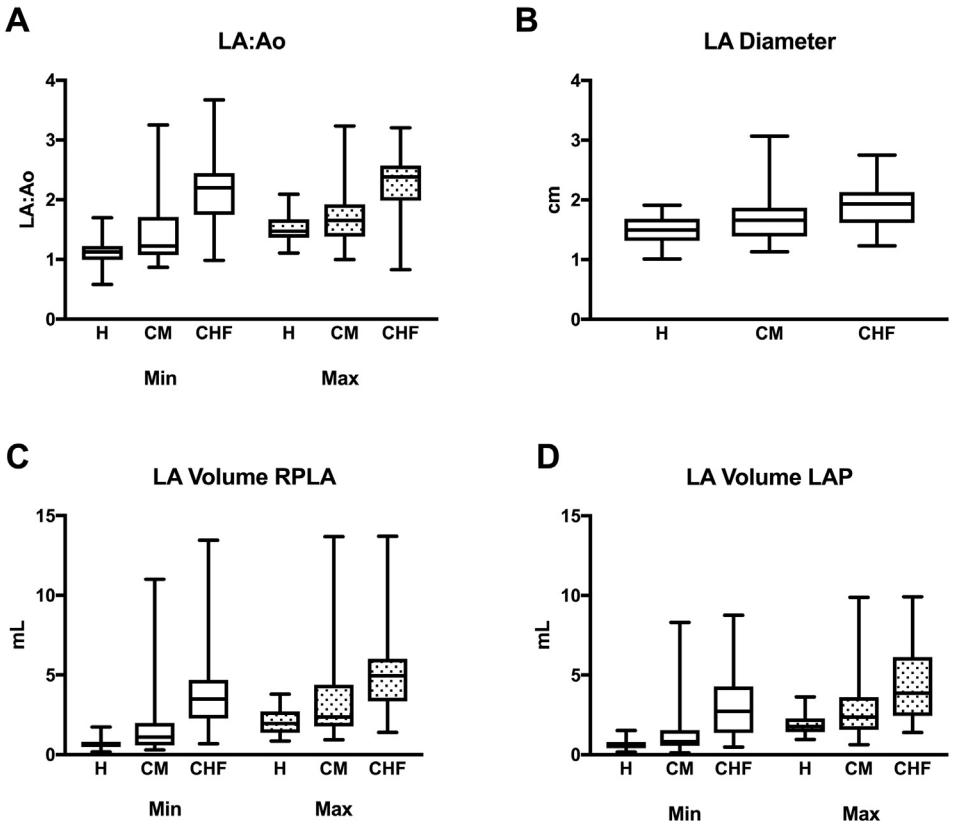

Fig. 2 Box and whisker plots of maximal and minimal LA linear and volumetric measurements in the H, CM, and CHF groups. The LA:Ao (A) and LAV (C and D) were measured at minimal and maximal values. The LAD (B) was measured only at the maximal time point. All group medians within time points were statistically different with the exception of the H and CM maximal LAV from the left apical view and the H and CM and the CM and CHF LAD comparisons. The boxes define the 25th and 75th percentiles, the median shown by the line, and the whiskers represent the minimum and maximum values. LA, left atrial; LA:Ao, left atrial-to-aortic ratio; LAD, left atrial diameter; LAP, left apical; LAV, left atrial volume; CHF, congestive heart failure; CM, cardiomyopathy; H, healthy; Min, minimum; Max, maximum; RPLA, right parasternal long axis.

from CHF cats. Using the cutoff of an $LA:Ao_{max} > 1.5$ [29] to identify LAE, there were 21 cats (34%) in the CM group that had a normal LA size and the remainder had LAE. The AUC for $LA:Ao_{max}$ to distinguish the CM cats with LAE from CHF cats was 0.7 and the optimal cutoff was 1.93 (sensitivity 82% and specificity 64%).

Discussion

The results of this study indicate that measurements of minimal LA size had higher AUC values to distinguish between cats with and without CHF compared to the corresponding maximum LA size values for every variable that had minimum and maximum values measured. Secondly, the measurements of LA size that best discriminated between cats with and without CHF were the $LA:Ao_{min}$, indexed $LAV_{min\text{-}LAP}$, and raw $LAV_{min\text{-}LAP}$, with $LA:Ao_{min}$ having a slightly better AUC than $LAV_{min\text{-}LAP}$.

In human and veterinary cardiology, LA size has, by convention, been measured at end ventricular systole when the LA functions as a reservoir and is at its largest size. Several recent human studies have correlated the minimum LAV with LV diastolic dysfunction, LV end diastolic pressure, and N-terminal pro—B-type natriuretic peptide values. Russo et al. [26] found that minimum LAV increased with early LV diastolic dysfunction, whereas maximum LAV only increased with late-stage dysfunction. In addition, their results showed a higher correlation between minimum LAV and E/E' and a higher AUC to identify diastolic dysfunction than maximum LAV [26]. Two additional studies found that minimum LAV had better correlation to catheter-derived LV end-diastolic pressure [27] and higher AUC to detect elevated N-terminal pro—B-type natriuretic peptide levels

Table 3 Receiver operator characteristic curve analysis to differentiate CM cats from those with CHF.

Variable	AUC	Threshold	Sensitivity %	Specificity %	P
$LA:Ao_{min}$	0.839	1.64	84.44	75.44	<0.0001
$LA:Ao_{max}$	0.8154	1.89	86.36	70.18	<0.0001
LAD (cm)	0.6593	1.68	72	50.91	0.023
$LAV_{min\text{-}LAP}$ (mL)	0.8235	1.46	75.53	75	<0.0001
$LAV_{max\text{-}LAP}$ (mL)	0.7276	2.46	76.47	58.33	0.0005
$LAV_{min\text{-}RPLA}$ (mL)	0.8073	2.35	76.92	79.63	<0.0001
$LAV_{max\text{-}RPLA}$ (mL)	0.7472	3.92	73.08	72.22	0.0004
$LAV_{min\text{-}LAP}$ (mL/kg)	0.8275	0.30	81.25	72.92	<0.0001
$LAV_{max\text{-}LAP}$ (mL/kg)	0.7376	0.68	71.88	68.75	0.0003
$LAV_{min\text{-}RPLA}$ (mL/kg)	0.8034	0.43	80.77	72.22	<0.0001
$LAV_{max\text{-}RPLA}$ (mL/kg)	0.7244	0.60	80.77	57.41	0.0012

AUC, area under the curve; CM, cardiomyopathy; CHF, congestive heart failure; $LA:Ao_{min}$, minimal left atrial-to-aortic ratio, measured at end-diastole just after the P wave; $LA:Ao_{max}$, maximal left atrial-to-aortic ratio, measured at early diastole at aortic valve closure; LAD, left atrial diameter measured at end-systole just prior to mitral valve opening; $LAV_{min\text{-}LAP}$, minimal left atrial volume from the left apical view measured at end-diastole just after the P wave; $LAV_{max\text{-}LAP}$, maximal left atrial volume from the left apical view measured at end-systole just prior to mitral valve opening; $LAV_{min\text{-}RPLA}$, minimal left atrial volume from the right parasternal long-axis view measured at end-diastole just after the P wave; $LAV_{max\text{-}RPLA}$, maximal left atrial volume from the right parasternal long-axis view measured at end-systole just prior to mitral valve opening.

[30] than maximum LAV measurements. Moreover, minimum LAV was found to have the highest correlation with heart failure hospitalization in a study of patients with diastolic dysfunction [31]. Minimal LAV is measured while the LA is exposed to LV diastolic pressure, while maximal LA size or volume may be affected by LV systolic function, LV systolic pressure, and mitral regurgitation, in addition to chronic exposure to LV diastolic pressures [21]. This may explain why the minimum LA size increases with early diastolic dysfunction and thus may be a better prognostic factor for CHF, arrhythmias, and cardiac death in patients with primarily diastolic dysfunction. As the most common cardiac diseases in cats result in predominantly diastolic dysfunction, minimal values of LA size may offer an earlier indication of elevated LV end diastolic pressure and progression towards CHF. That being stated, the addition or replacement of any echocardiographic measurement should follow rigorous evaluation in multiple studies with diverse populations to ensure it adds clinically useful information to warrant the time required to perform the measurement. The results of our study indicate that minimum values of LA size are statistically superior to differentiate cats with and without CHF and additional studies are warranted to assess if this information is clinically superior as well.

In our study, volumetric measurements of LA size were not superior to linear measurements to distinguish cats with and without CHF. This is discordant with findings from studies conducted in humans and dogs comparing these measurements. Volumetric measurements of LA size have effectively replaced linear measurements in human cardiology, and the biplane MOD is the recommended method to obtain LAV by the American Society of Echocardiography [20]. These recommendations note that while linear measures of LA size are frequently used clinically, the LAD does not 'represent an accurate picture of LA size' [20]. Recent studies of LA size in dogs have shown discrepancies between values determined by LAV versus LA:Ao, with LAV being superior in identifying mild LAE [23]. More recently, Toaldo et al. [32] found that LAV was a better predictor of cardiac death compared to LA:Ao in dogs with myxomatous mitral valve disease.

While the body of evidence for recommending the use of LAV for LA size assessment in humans and dogs continues to grow, the results of this study would indicate the same may not be true for cats. Possible reasons for our discrepant results in this species could be our method of measurement in that we used monoplane rather than biplane MOD, which may have yielded less accurate measurements of LA size. We chose to use the monoplane MOD since we felt this would be more clinically relevant as biplane MOD may be too time consuming for practicing veterinary cardiologists. In addition, the 2-chamber LAP view can prove challenging to acquire in awake, unsedated cats, hindering the clinical use of biplane MOD. Monoplane and biplane measures of LAV in humans were found to be highly correlated with a small bias of 1.9 mL/m^2 [33], but even a small difference may be more substantial in the relatively small volumes of cat atria. Ultimately, our LAV values for cats were similar to those previously published by

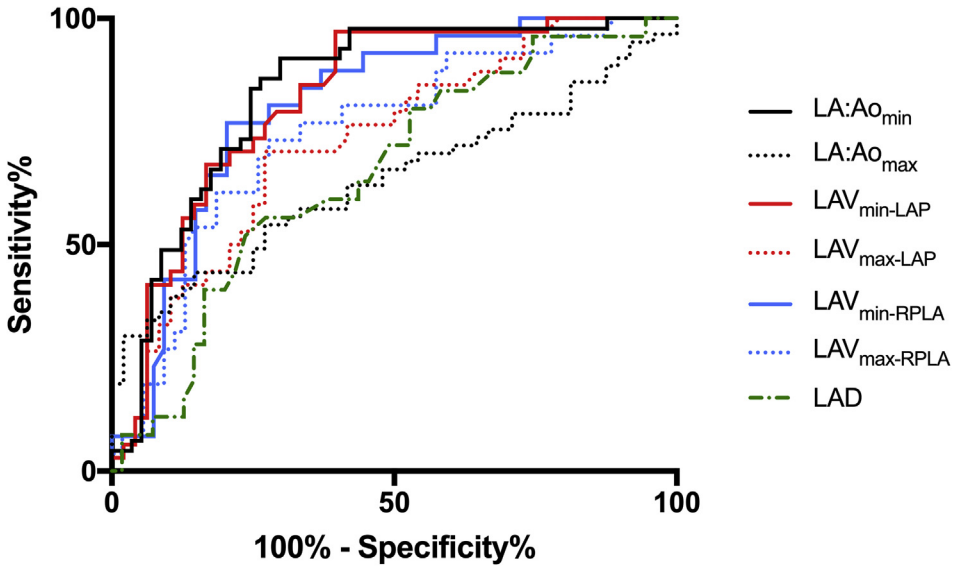

Fig. 3 Receiver operator characteristic curves to distinguish cats with primary cardiomyopathy without congestive heart failure from those with congestive heart failure. Minimal values of left atrial size and volume showed larger areas under the curve than each corresponding maximal value. LA:Ao, left atrial-to-aortic ratio; LAD, left atrial diameter, LAP, left apical; LAV, left atrial volume; Max, maximum; Min, minimum; RPLA, right parasternal long axis.

Linney et al. [24], indicating the difference may not be due to solely a measurement error in our study.

Alternatively, it is also possible that the LA enlarges differently in cats compared to dogs or humans. This may be supported by differences in appearance of LAE on thoracic radiographs in cats compared to dogs [34]. While dogs frequently display dorsal deviation of the caudal cardiac border on lateral radiographs with even mild LAE, this finding is less frequently noted in cats, especially those with mild or moderate LAE [16]. The superiority of LAV for assessing LAE in dogs and humans has historically been attributed to the fact that LAV better represents LAE in multiple planes. If LAE in cats occurs primarily in the lateral or anterio—posterior planes, this could explain why the LA:Ao linear measurements displayed better AUC values than LAV measurements, although would fail to explain the comparatively poor performance of the LAD in our study. The discrepant performance of the LA:Ao and LAD measurements could be due to the different imaging planes these measurements are performed on or because the weight-independent LA:Ao [29] accounts for varying body size via the aortic index and therefore has less overlap between groups.

While the LA:Ao$_{max}$ and LA:Ao$_{min}$ linear measurements both had high AUCs for distinguishing cats with and without CHF, the LAD had the lowest AUC of all measurements made in this study. This is in concordance with findings from human studies and the recommendations of the American Society of Echocardiography [20]. Although volumetric measurements were not superior to linear measurements in our study, it may be concluded from our results that both LA:Ao and LAV offer better assessments of LA size than LAD in cats. Our results of LAV are similar to those published by Linney et al. [24] from the RPLA view, further establishing that LAV measurements are feasible in cats. In our study, values of LAV from the RPLA and LAP views were statistically different, despite a relatively small difference in their median values. The RPLA values were slightly larger than the LAP values, and we suspect this may be due to an underestimation of LA size from the LAP, possibly from less clear endocardial border visualization. Alternatively, although we strove to utilize only images that excluded the aorta, it is possible that one of the two views provided better alignment with the true long axis of the LA affecting the measurements. We concluded that, while similar, values from the RPLA and LAP views are not interchangeable for LAV in cats. Owing to the difficulty in obtaining high-quality LAP images in some cats and the higher likelihood of obtaining measurable images from the RPLA, future studies of LAV in cats may benefit from focusing solely on LAV from the RPLA.

Based on the ROC analysis, an LA:Ao$_{min}$ of 1.64 had the best combined sensitivity and specificity to distinguish between occult CM and CHF cats. The LAV$_{min-LAP}$ raw and body weight indexed values with optimal sensitivity and specificity to distinguish CM and CHF cats were 1.46 mL and 0.3 mL/kg,

respectively. Interestingly, the body weight indexed values of LAV appear slightly smaller in healthy cats than those reported in healthy dogs. The median LAV_{max} of healthy cats from the RPLA was 0.46 mL/kg in our study, while reported values for dogs have been 0.58 mL/kg [35] and 0.89 mL/kg [23]. Whether this represents a true species difference in the LAV of healthy veterinary patients or due to the specific populations or methodology used will require further study.

This study has several limitations that should be considered when interpreting the results. First, the retrospective nature of the study has inherent limitations. Several observers with a range of experience acquired the echocardiographic studies, although image acquisition by residents in training was actively supervised by a board-certified cardiologist. In addition, images were not acquired with volumetric LA measurements in consideration; therefore, the images were not optimized for these measurements and a prospective imaging study may have different results. Secondly, some cats were administered cardiac medications prior to echocardiographic evaluation. In particular, 37 cats, including 9 in the CM and 28 in the CHF groups, had received oral or parenteral furosemide within 24 h prior to echocardiography. Theoretically, diuretic therapy could alter LA dimensions and pulmonary venous size, potentially leading to a false-negative diagnosis of CHF and underestimation of LA dimensions. However, two studies performed in dogs failed to reveal significant changes in LA:Ao before and after parenteral or oral furosemide administration [36,37]. Unfortunately, there are no published data available in cats on if and how much LA size may change following diuretic therapy and whether any changes may be dose dependent or atrial size dependent. Some studies have identified medication effects including a mild decrease in LAD without an effect on LA:Ao after atenolol therapy [38], while others have found no effects of either atenolol or pimobendan on LA size in cats [39—41]; thus, we chose to not exclude cats due to medication history. We strove to exclude cats with right-sided or biventricular failure based on the presence of severe, subjective right atrial enlargement, although some cats without severe right atrial enlargement had fluid accumulations that could have been due to concurrent right-sided heart failure.

Importantly, the timing within the cardiac cycle of the maximum measures of LA size was not equivalent. The $LA:Ao_{max}$ measurement was performed at early ventricular diastole, just following the aortic valve closure, while the maximal LAV measurements were performed at end ventricular systole, just prior to the mitral valve opening. Theoretically, the time between these points in the cardiac cycle, and therefore these two measurements, should only include the isovolumetric relaxation time in which minimal change would be expected in LA size. However, without the mitral valve in view in the right-sided short-axis images, measurement of the LA:Ao prior to the mitral valve opening could not be confirmed. Despite this limitation, the authors feel these measurements offer a clinically achievable comparison of methods to assess maximum LA size. Lastly, only monoplane measurements of LAV were made, while biplane measurements are recommended and known to be more accurate compared to volumetric gold standard imaging such as cardiac magnetic resonance imaging or computed tomography. Unfortunately, the retrospective nature of the echocardiographic images did not include a two-chamber LAP view on most studies to allow a biplane method to be used.

Conclusions

The results of our study provide further evidence that LAV measurements are feasible in cats with superior performance of minimum LA size and volume measurements to differentiate cats with and without CHF. This is in contrast to the most commonly used time point to measure the LA size in veterinary medicine. Left atrial volumes were not superior to LA:Ao to distinguish between cats with and without CHF. Additional studies to assess the prognostic value of minimum LA size and volumes in cats with cardiac disease are warranted.

Conflicts of interest statement

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

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Supplementary data

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