Title: Echocardiographic reference intervals in healthy UK Deerhounds and prevalence of preclinical dilated cardiomyopathy: a prospective, longitudinal study.

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Abstract

Background: Sighthounds have high echocardiographic (ECHO) left ventricular volumes. Establishing robust breed-specific ECHO reference intervals (RI) for screening is important. End-diastolic volume index (EDVI), end-systolic volume index (ESVI) and ejection fraction (EF) reference ranges derived by Simpson's method of discs are not available for Deerhounds. The influence of sex or body weight (BW) on left ventricular diameter during diastole (LVDd) and systole (LVDs) has never been reported.

Objectives: Prospectively determine ECHO RI and assess prevalence of dilated cardiomyopathy (DCM) in healthy UK Deerhounds.

Animals: Ninety-nine Deerhounds.

Methods: Deerhounds scored on ECHO and ECG variables then classified as normal (NORM), equivocal (EQUIV) or affected (AFF) with DCM. Fifty-nine NORM Deerhounds used to determine ECHO RI.

Results: Prevalence of DCM was 21.6%. There were significant differences in BW ($p<0.001$), LVDd ($p<0.001$) and LVDs ($p<0.05$) between female and male Deerhounds. Cut-off values for EDVI ($\geq$140.2mL/m^2: 79% sensitivity/97% specificity), ESVI ($\geq$71.9mL/m^2: 94.7% sensitivity/94.2% specificity) and EF ($\leq$42.1%: 84.2% sensitivity/92.8% specificity) were proposed to help diagnose DCM. The most reliable ECHO variables to identify AFF dogs were LVDs indexed to BW by allometric scaling and ESVI; one of the least reliable was sphericity index. Ventricular arrhythmias (VA) were identified in 13.6% of the population, with the highest prevalence in AFF Deerhounds (42%).

Conclusions: Preclinical DCM in Deerhounds is common and VA may be associated with DCM. Healthy Deerhounds have higher LVDd, LVDs and EDVI compared with other breeds. This study provides ECHO RIs for Deerhounds; sex or BW RIs should be used when screening.

Key words: Ventricular arrhythmia, sighthound, left ventricular volume.

Abbreviations	
Ao	aortic
AF	atrial fibrillation
AFF	affected group
AUC	area under the curve
BSA	body surface area
BW	body weight
DVD	degenerative valve disease
d	diastole
DCM	dilated cardiomyopathy
ECHO	echocardiography
EF	ejection fraction
ET	ejection time
EDV	end-diastolic volume
EDVI	end-diastolic volume index
ESV	end-systolic volume
ESVI	end-systolic volume index
EPSS	E point-to-septal-separation
EQUIV	equivocal group
FS	fractional shortening
IWHs	Irish wolfhounds
NORM	healthy group
KC	kennel club
LA	left atrial
LA/Ao	left atrium/aorta ratio
LV	left ventricular
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
LVD	left ventricular internal diameter
PEP	left ventricular pre-ejection period
n	normalised for body weight
RI	reference intervals
ROC	receiver operator characteristic
SMOD	Simpson's method of discs
SPHI	sphericity index
s	systole
2D	two-dimensional
VA	ventricular arrhythmias
Vmax	maximum flow velocities
VPC	ventricular premature complex

Introduction/Objectives

Establishing breed-specific echocardiographic reference ranges is vital to enable accurate and early diagnosis of dilated cardiomyopathy (DCM). Left ventricular volumetric measurements have been shown to be important for the early detection of preclinical DCM and superior to M-mode for detecting early changes [1]. There have been no studies in Deerhounds establishing reference intervals (RI) for left ventricular volume measurements calculated by Simpson's method of discs (SMOD) indexed to body surface area (BSA) for left ventricular end-diastolic volume (LVEDV/BSA), end-systolic volume (LVESV/BSA) or ejection fraction (EF) derived from SMOD. A previous study has reported on M-mode reference values, including Teichholz formula to determine LVESV/BSA and EF [2]. However, the Teichholz formula uses the minor axis diameter of the left ventricle to determine left ventricular volumes. This can significantly over-estimate volumes if left ventricular geometry is abnormal, with a rounded chamber, although EF is less affected by geometrical assumptions [3]. To enable early and accurate diagnosis of preclinical DCM in this breed, it is important to detect early volumetric echocardiographic changes in Deerhounds. Establishing robust breed-specific echocardiographic RI is therefore vital in maintaining the health and future for this breed and will help establish a scheme for breed screening in the UK. Similar to other sighthound breeds, it could be hypothesised that Deerhounds have high heart size to body weight (BW) ratios, as has been shown in other sighthounds such as Salukis and Whippets [4, 5]. This could be expected in view of their athletic nature and the large volumes of blood required quickly during deer coursing, the work they were originally bred for. The pursuit and hunting of deer is no longer permitted in the UK, however the strength and speed of the Deerhound is ideally suited for such work. This large breed has now been classified as “vulnerable” according to the UK Kennel Club (KC), with only 172 KC registered Deerhound puppies in 2019.

A published survey demonstrates that in the UK Deerhound population, the most common cause of death are cardiac causes which represent 24% of all death [6]. A 2014 KC survey also listed cardiac failure and cardiomyopathy as the most common causes of death in UK Deerhounds [7]. It is likely that the acquired heart disease DCM is contributing towards this high rate of death amongst Deerhounds. It has been shown that Deerhounds have the highest prevalence of DCM of any breed at 6% (7/117) of hospital admissions [8]. It is apparent that a cardiac cause of mortality and DCM, are common in Deerhounds. The primary aim of the study was to establish echocardiographic RI, including SMOD measurements, in clinically healthy UK Deerhounds. The secondary aim was to establish the prevalence of preclinical DCM in the group of clinically healthy Deerhounds. The hypotheses were that DCM-free Deerhounds had high heart size to body size ratios and that a significant proportion of apparently healthy Deerhounds were affected with DCM.

Animals, Materials and Methods

Enrolment of dogs

A cohort of asymptomatic Deerhounds was evaluated mainly at dog shows but also at veterinary practices throughout the UK by the principal investigator (ED) and one author (JH) between 2014 and 2020. Owners and breeders across the UK were invited to bring presumed healthy hounds of at least four years of age for screening as the

Deerhounds were to be followed longitudinally. They had to provide five-generation pedigree documents provided by the UK KC. The hounds were all examined at least once and repeat echocardiography at least 12 to 24 months later was advised at the primary examination, although this was not compulsory. The study was approved by The Animal Health Trust Ethics committee (29-2013). Owner consent was obtained for this prospective study.

Exclusion Criteria

Dogs diagnosed with congenital heart disease were excluded. Any dog identified as having preclinical DCM, with a dilated left ventricle and systolic dysfunction, had their data collected and classified as affected (DCM-affected). Any hounds with evidence of serious systemic illness on examination were excluded. Any Deerhounds without five-generation pedigree KC documents were excluded. Any dogs diagnosed with other acquired heart disease, such as degenerative valve disease (DVD), during the initial examination (with the exception of DCM-affected dogs) were excluded. The DVD was diagnosed by examining valve leaflets and identifying leaflet thickening or valve prolapse with evidence of valvular regurgitation using colour flow Doppler mapping. Dogs diagnosed with DVD at their second or third examination (therefore older dogs), but not during their first examination, had their echocardiographic values removed from the study at the date the DVD was diagnosed. Their initial echocardiographic values (when DVD was not present) were, however, included.

Clinical examinations and echocardiography

All hounds underwent a clinical examination and the results, including BW (kg), sex and neuter status were recorded. For those Deerhounds assessed at dog shows, owners were asked to weigh their dogs during the week prior to the show. Their weights were recorded and BSA ($0.101X[BW]^{2/3}$) calculated in m^2. Those hounds examined at veterinary practices had their weights and calculated BSA recorded that day. All dogs underwent echocardiography without sedation and in the standing position [9, 10] from both right and left sides using a 1.5-3.6 MHz probe[a] with harmonic imaging and with a simultaneous ECG recording. Examination procedures followed the recommendations proposed by the Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine [11] using a previously validated technique [9, 10]. Two-dimensional (2D), M-mode, colour and spectral Doppler assessments were completed. A minimum of three cardiac cycles were measured and the results were averaged for each dog. Comprehensive echocardiographic examinations were performed at each evaluation. Thyroid function testing was initially undertaken only in those dogs with clinical suspicion of hypothyroidism although during the last 12 months of the study, testing was offered to all patients.

Simpson's Method of Discs

Right parasternal long-axis and left apical four-chamber views were obtained to calculate SMOD-derived end-diastolic volume (EDV) and end-systolic volume (ESV) measurements, Figure 1. Every attempt was made to include the LV apex and optimise the LV length and area. Both right parasternal and left apical views were measured and the larger volumes used, to reduce potential volume underestimation [12, 13]. The left ventricular (LV) area was measured by tracing the endocardial border on each selected image. The maximal LV length was measured from the middle of a line connecting the mitral annulus to the endocardial border of the LV apex. Frame-

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[a] GE Vivid Q echocardiography machine GE medical systems Buckinghamshire, UK

by-frame analysis permitted selection of end-diastolic frames (defined as onset of the QRS, corresponding to the time of mitral valve closure) and end-systolic frames (defined as the last frame before mitral valve opening). The EDV and ESV were then automatically calculated and indexed to BSA to produce EDVI and ESVI measurements. The LV EF was calculated using the SMOD-derived LV volume measurements.

M-mode and 2D-derived measurements

M-mode measurements were obtained from the right parasternal short-axis view with the cursor symmetrically bisecting the left ventricle at the level of the insertion of the chordae tendinae. It was ensured that the LV was horizontal (not tipped) on the right parasternal long-axis view before rotating the probe for the right parasternal short-axis view. The following variables were obtained from M-mode images of the right parasternal short-axis view: interventricular septum thickness, left ventricular internal diameter (LVD), and left ventricular free wall thickness in systole (s) and diastole (d). These were normalised for BW by allometric scaling [14] and LVDdn and LVDsn indices recorded. Fractional shorting was calculated as (LVDd-LVDs / LVDd) x 100%. From a mitral valve M-mode, the mitral E point-to-septal-separation (EPSS) was measured. From a 2D right parasternal short-axis view, the left atrial (LA) diameter and aortic root diameter (Ao) were measured immediately after closure of the aortic valve (early ventricular diastole). The following variables were then calculated: the left atrium/aorta ratio (LA/Ao) [15], fractional shortening (FS), and sphericity index (SPHI) calculated by LV length/LVDd [16]. Left atrial maximal diameter from a long axis 4 chamber view at end-ventricular systole (last frame before mitral valve opening) [15] was recorded.

Doppler-derived measurements

Maximum flow velocities across the aortic and pulmonary valves (Vmax aorta and Vmax pulm) were obtained from spectral Doppler profiles. The Vmax aorta was measured from the left apical 5-chamber plane rather than from the subcostal view due to the hounds being in a standing position. Valves were interrogated for regurgitation using colour flow Doppler mapping, with colour gain set just below speckling artefact, using optimised views depending on the valve. Regurgitation was subjectively classified as trace, mild, moderate or severe [17, 18]. If tricuspid regurgitation was identified then maximal tricuspid regurgitation velocity was recorded using CW Doppler. Angle correction was not used for any spectral Doppler recording but every attempt to optimize alignment was made. If mitral regurgitation was present, staging was performed by estimating the ratio of the mitral regurgitant jet area and the left atrium area [19]. Regurgitation was considered to be mild if the jet size was <30% of the left atrial area, moderate if it was 30-70% and severe if >70% of the left atrial area [20]. From the left apical 5-chamber view, optimising aortic flow and from spectral Doppler of aortic flow, left ventricular pre-ejection period (PEP) was recorded as the time between the onset of the Q-wave until aortic valve opening recorded on the spectral trace. Ejection time (ET) was recorded as the time between opening and closure of the aortic valve on the spectral trace [21] and LV PEP:ET was then calculated.

Any arrhythmia, including ventricular or supraventricular arrhythmias, identified during the echocardiogram was noted and a six-lead ECG examination and 24 hour ECG (Holter) monitoring offered. During the last 12 months of the study, a 24 hour Holter was offered to all Deerhounds scanned, regardless of whether an arrhythmia had been detected during screening. Any cases with atrial fibrillation (AF) had average heart rate over the length of the ECG trace noted. Dogs were classified as having ventricular arrhythmias (VA) if one or more ventricular premature complex (VPC) was identified during the echocardiogram. Malignant VA were classified as greater than or equal to 100 VPCs in 24 hours, with the presence of couplets, triplets, or runs of ventricular tachycardia.

Scoring and Categorising into Groups

Scoring was carried out as described by the ESVC Taskforce [16]. Cut-off values for echocardiography (ECHO) parameters were determined using published data [2, 16]. Major criteria (three points each) were LVDd >56 mm [2], LVDs >39.1 mm [2], SPHI<1.65 [16], either FS<20% [2] and/or EF<40% [16]. Minor criteria (one point each) included VA, AF, EPSS >0.94 cm [2], PEP:ET>0.54 [22], equivocal FS (20-25%) [2], left (LA:Ao>1.6) or biatrial enlargement [15]. Dogs scoring three points or fewer were considered healthy (NORM), dogs scoring four or five were considered equivocal (EQUIV), and dogs scoring six or more were considered affected (AFF). For dogs with multiple ECHO examinations, the data and score from the most recent ECHO only were used in the analysis and as the final diagnosis. Data from the second (or last in those cases which were examined more than twice) ECHO examination were used to create the RI for the clinically healthy ("NORM") dogs. The exception was those Deerhounds which developed DVD. The Deerhounds which developed DVD had their ECHO values used from the last normal ECHO exam prior to DVD diagnosis, in other words from their penultimate ECHO exam.

Statistical Methods

Statistical analysis was carried out using standard commercial software[bc]. Data were examined using basic descriptive statistics. Comparisons of categorical variables between groups used the Fisher's Exact Test and Pearson's Chi-square test as appropriate. Histograms, quantile plots and the Shapiro-Wilks test were used to check if continuous variables adequately fulfilled the distributional assumptions required for parametric analysis. Variables which obeyed the required assumptions were compared with independent t-tests and one-way ANOVA; those which did not were compared using the Kruskal-Wallis or Mann-Whitney Rank Sum tests. Suggested RI were obtained following ASVCP guidelines [23] for samples between 20 and 120 samples. Variables were checked for outliers and corrected as necessary, and observations were transformed if required to meet the assumptions of a Gaussian distribution. The 95% RI between the 2.5 and 97.5 centiles was estimated as +/- two standard deviations above the mean and 90% confidence intervals were derived using parametric methods. Variables which had been transformed for analysis were back-transformed to their original units for the display of results. Statistical significance was set at $p<0.05$ and adjustments for multiple comparisons used the methods of Dunn and Holm-Sidak as appropriate.

The ability of each ECHO variable, in particular the SMOD measurements, to diagnose DCM was investigated by generating receiver operator characteristic (ROC) curves with AFF dogs being considered positive and the combined group of NORM/EQUIV being considered to be negative; area under the curve (AUC) reported for each. Separate curves were generated for each sex for LVDd and LVDs. Although not used

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[b] SigmaPlot ® 12 software (Systat Software Inc, London, UK)
[c] STATA16 (Statacorp, College Station, TX, US)

within the scoring system, ROC curves were also generated for ESVI and EDVI to assess the utility of these ECHO variables in the identification of AFF dogs. Approximate optimal cut-off values were obtained from the ROC plots to distinguish AFF dogs from NORM and EQUIV dogs for each ECHO variable. Two sets of exact cut-off values were chosen a) to maximise the test sensitivity and b) to maximise the test specificity. The cut-off values were compared to those suggested in previous studies [2, 4, 12, 13, 32, 33, 34].

Results

A total of 99 Deerhounds were examined on at least one occasion. Of these, based on the assessment data included in the study, 59 were classified as DCM-free (NORM group), 19 were DCM-affected (AFF group) and 10 were equivocal (EQUIV group). Of the 99 Deerhounds, 11 were excluded as they failed to meet the entry criteria (two had no five-generation pedigree; one was under four years of age; eight had DVD during the first ECHO examination). The remaining 88 hounds were therefore included in the analysis. The ages of the 88 hounds ranged from four to 11.25 years. Thyroid function was assessed in 32/88 dogs (36%); none were diagnosed with hypothyroidism. One EQUIV dog was being treated for hypothyroidism at the time of screening and clinical signs and serum thyroxine concentrations were well controlled and had been for ten months. No dogs were receiving cardiac medications at the time of screening. The prevalence of DCM based on score was 21.6%.

There was no significant difference in age (p=0.118), sex (p=0.32), neutered status (p=0.22) or BW (p=0.803) between the three groups. There were significant differences in ECHO variables between groups (Table 1). Of the 59 DCM-free hounds, 27 were male (four neutered) and 32 were female (13 neutered). Median age of NORM was 6.2 years (range; four–11.25 years) and median BW of NORM was 42.2 kg (range; 30-63.9 kg). The BW of NORM females (median 38.3 kg; range 30-63.9 kg) was significantly less than the NORM males (median 45.4 kg; range 30.1-58 kg); p<0.001.

Of the NORM Deerhounds, 31 scored one major criterion, 30 of which had decreased SPHI and one had low fractional shortening (19.2%); the remaining dogs scored only minor criteria or zero. Of the EQUIV hounds, all scored 4-5 points on the basis of impaired systolic function or reduced SPHI plus one or two minor criteria. Thirty-five of 88 (40%) Deerhounds had one repeat ECHO examination and 8/88 (9%) hounds had two repeat ECHO examinations. The mean time interval between the repeat ECHO examinations was 24.9 months. Of the 43/88 (49%) hounds which were screened two or more times during the study period (34 NORM, eight EQUIV, one AFF), three moved from EQUIV to AFF group, four moved from NORM to AFF, four moved from EQUIV to NORM group, three moved from NORM to EQUIV group. The remaining dogs did not move groups (27 NORM, one EQUIV, one AFF), Figure 2. Three of the ten dogs which progressed (from NORM to EQUIV or AFF, or from EQUIV to AFF) had VA during the ECHO. Of the 19 AFF hounds, 12 were diagnosed as AFF on initial ECHO exam and 11 did not have repeat ECHO. Five of those 12 had VA (single VPCs) during ECHO and one had AF. The prevalence of VA during ECHO for all 88 hounds was 13.6%. Holter monitors were fitted to 31 hounds (19 NORM, 4 EQUIV, 8 AFF). There was a significant difference in proportion of VA between groups with more AFF dogs having VA (8/19; 42%) than EQUIV (3/10; 30%) than NORM (1/59; 2%) (p<0.001). Of the 8/19 AFF dogs with VA, all eight had single VPCs, four

Deerhounds had couplets, two had triplets and two had ventricular tachycardia (some episodes with R on T phenomenon). The median number of VPCs/24 hour was 500 (range 10 - 42,046 VPCs/24 hour). Of the 3/10 EQUIV dogs with VA, all three had single VPCs, two had couplets, one had one triplet and there were none with ventricular tachycardia. The median number of VPCs/24 hour was 1,106 (96 – 2,115 VPCs/24 hour). The one NORM dog with VA had a single VPC during the ECHO only and had no VA during the Holter analysis. Only one dog presented with AF (group AFF) and had significant left atrial dilation. The average heart rate for this AFF dog with AF was 100 bpm.

Data from 59 NORM hounds (27 males, 32 females) were used to calculate suggested RI for ECHO parameters in normal Deerhounds (Table 2) and to investigate possible differences between male and female hounds. Eleven hounds (18%) were less than five years of age. Thirty-one hounds finally classified as NORM had been scanned at least twice, of which three hounds had three scans. The BW ($p<0.001$), LVDd ($p<0.001$) and LVDs ($p<0.05$) of NORM females were significantly lower than NORM males. When the LVDd and LVDs values were allometrically scaled to BW, LVDdn and LVDsn between sexes were not significantly different ($p>0.066$). The ECHO parameters with the highest AUC from the ROC curve analyses to identify AFF dogs, and which were not classification criteria (i.e. not part of the ESVC scoring system), were LVDsn and ESVI (Table 3 and Table 4). The variables (both those part of the ESVC scoring system and those not included in the scoring system) with the lowest AUCs were LA/Ao, SPHI and PEP:ET (Table 3 and Table 4).

Discussion

This study reports the ECHO findings of a large population of UK Deerhounds with and without evidence of preclinical DCM. The prevalence of DCM in the Deerhounds was 21.6%, a significant proportion of which had VAs; findings never previously reported in this breed. The group of NORM dogs was used to generate an updated RI, including volumetric ECHO measurements, and to highlight the differences in BW, LVDd and LVDs between male and female hounds. Our data suggest that sex or BW should be taken into account during screening Deerhounds. This study also suggests RI for Simpson's EF, EDVI, ESVI and SPHI, none of which have ever been reported or evaluated before in this breed. Deerhounds appear to have high LV size to BW ratio when compared to other breeds.

The prevalence of DCM in this population of hounds (21.6%) was similar to the prevalence (6/27; 22.2%) in a previous, much smaller study [2]. The 21.6% prevalence was also similar to the figure stating that cardiac causes represent 24% of all death in UK Deerhounds, assuming that DCM was the greatest contributor [6, 7]. The prevalence of DCM in Irish wolfhounds (IWHs), often quoted as a closely related breed to the Deerhound, was relatively similar and reported as being between 24.2 and 29% [24, 26, 37]. This study contains a large number of older Deerhounds compared to any previous study of this breed [2]. The fact that hounds were repeatedly screened to assess progression and were older, increased confidence in ensuring correct phenotypic classification in this study. Sighthound breeds are athletic and known to have large volume hearts compared to other dog breeds, highlighting the importance for obtaining breed-specific reference ranges so as not to misdiagnose DCM echocardiographically [2, 4, 5, 28]. As with previous studies in other breeds, ESVI was shown to be a reliable indicator to identify AFF Deerhounds [1, 12, 13]. As also previously found in other breeds, the median ESVI in NORM Deerhounds (50.5 mL/m^2)

was found to be higher than a previously suggested value 30 mL/m^2 [16]. The reported cut-off to identify AFF Deerhounds in this study was 71.9 mL/m^2; this was similar to a previously reported value of 70 mL/m^2, albeit derived from the Teichholz formula [2]. In Doberman pinschers, the suggested cut-off was lower at >55 mL/m^2, again this difference in value highlights the need for breed specific RI [12]. Diagnosing DCM early on in the disease process may be important as there is evidence in Doberman pinschers and IWHs that treatment in the preclinical stage of DCM prolongs time until onset of heart failure and extends survival [26, 27].

The median EDVI (112 mL/m^2) calculated in this study for NORM hounds highlights how Deerhounds have large volume hearts normally. Whippets and salukis have been previously reported as having median EDVI 85 mL/m^2 and 97 mL/m^2 respectively [4]. It may be that Deerhounds have higher EDVI values due to the endurance exercise and work they were originally bred for. Whippets were bred for short distance running at high speed; Deerhounds for hunting red deer by coursing all day. This could be likened to human long distance runners, with long distance athletes having larger volume hearts than strength-trained athletes due to the cardiovascular effects of endurance exercise [29, 30]. Also, in Alaskan sled dogs, an increase in EDVI by 8% was shown following endurance training [31]. We hypothesise that the high left ventricular volumes in Deerhounds is genetic rather than attributed to training alone as Deerhound coursing is illegal in the UK and most of the study population are show dogs. However this was not one of the aims of the study and further studies would be required to prove this hypothesis. Our results provide, for the first time, a proposed EDVI cut-off >140.2 mL/m^2 to help diagnose DCM in Deerhounds, however this would need to be validated in a separate study. It has been suggested in Doberman pinschers that an EDVI cut-off >95 mL/m², in addition to elevated ESVI, should be used to help diagnose DCM in the breed [12]. This marked difference is, once again, likely due to Deerhounds having large volume hearts, as with other sighthound breeds [4, 28].

Our results show significantly smaller LVDd and LVDs values were identified in female hounds compared to male hounds, as shown in other breeds, such as Doberman pinschers, boxers and great Danes [12, 13, 33]. This difference was no longer significant when the values were allometrically scaled to BW. Sex or BW should therefore be taken into account during screening Deerhounds, as highlighted by our results. Previously published RI combined values for male and female Deerhounds rather than separating them out according to sex or BW. An interesting finding was that the suggested LVDd and LVDs cut-off values in Deerhounds are higher than those suggested for great Danes, despite a large difference in BW between both breeds [33]. The mean BW of the NORM Deerhound in this study is 43.1 kg and in the great Dane study, a mean BW 64.3 kg was reported among the NORM dogs.

The SPHI values in this study led to 30/31 hounds scoring a major criterion. However, SPHI was shown in the results of this study to be one of the least useful predictors for identifying AFF dogs, despite being an inclusion criterion. This calls into question whether SPHI should be relied upon as a major criterion, as suggested it should be by the ESVC DCM guidelines [16]. A previous study examining SPHI and EPSS in Doberman pinschers also questioned the value of SPHI during the ECHO exam [32]. The cut-off proposed in Deerhounds (1.53) was lower than 1.65 proposed in previous studies involving Doberman pinschers, great Danes and also suggested by the ESVC

DCM guidelines, although the latter cut-off value was published without an evaluation study, other than with Newfoundlands [16, 32, 33]. In the current study, the sensitivity for a SPHI cut-off 1.65 is low at 29.4%, with a specificity value of 89.5%. The suggested cut-off for Deerhounds (1.53) has a higher sensitivity (61.8%) than when using the 1.65 cut-off value but the specificity is lower (79.0%). The lower than expected SPHI cut-off value 1.52 suggests that perhaps Deerhounds normally have more rounded left ventricular chambers than most other breeds therefore have low SPHI values (normally) compared to other breeds, as has been shown in English springer spaniels [34]. This new finding that Deerhounds may have a different SPHI cut-off to most other dog breeds is important to know and highlights the importance of evaluating RI in individual dog breeds. The new cut-off is also in accordance with the hypothesis that Deerhounds have large rounded hearts compared to other dog breeds. The geometrical shape (or sphericity) of the left ventricle will vary between dog breeds and further studies are required examining various shapes in various dog breeds with and without heart disease. It is possible that the lower than expected SPHI values may have been due to slight overestimation in LVDd measurements, or slight underestimation in LV length, as in general for ECHO of SPHI, but possibly a greater risk due to the Deerhounds being scanned in the standing position. This would need to be verified in a separate study whereby SPHI values were calculated by measuring LVDd with the Deerhounds positioned in right lateral recumbency and compared to the values obtained in this study. However every attempt to avoid these measurement errors was made during each ECHO study. Examining the spread of the SPHI values also showed that there was a lot of overlap between the NORM and AFF groups which was probably why it performed badly as a discriminatory test.

A proposed cut-off value for Simpson's EF has been established in this cohort of Deerhounds as 42.1% with a sensitivity of 84.2% and specificity of 92.8%; or 46.1% if sensitivity is maximised to 94.7% (with a specificity value of 81.2%); Table 3. The median EF in NORM Deerhounds is 53.7%, slightly higher than English springer spaniels, Doberman pinschers, salukis and boxers but similar to great Danes and slightly lower than whippets [1, 4, 13, 33, 34, 35]. A previously reported mean EF for Deerhounds (54.3%) was measured by the Teichholz method as opposed to the Simpson's method used in this study [2]. The suggested cut-off value of >0.61 for PEP:ET (Table 4) obtained in this study may be higher than expected. This may be a breed related difference or could be due to the method used calculating this value in that only three cardiac cycles were measured and the results averaged. As heart rate can affect PEP:ET value, one study suggests measuring at least ten cycles when calculating PEP:ET to help minimise the effect of heart rate [36]. The published PEP:ET reference ranges are usually from aortic M-modes and the M-mode temporal resolution may be superior than possible ECHO software delay in displaying the spectral Doppler signal following the QRS complex of the ECG [22, 36]. Reference ranges for spectral Doppler and M-mode may not be interchangeable. In this study, PEP:ET ratio was one of the least useful predictors for identifying AFF dogs.

Atrial fibrillation has been described in the absence of obvious cardiovascular disease in large and giant breeds such as IWHs [38]. In view of Deerhounds being a large breed and described as possibly closely related to IWHs, it may be expected that subclinical AF should be common and perhaps as frequent in Deerhounds as it is in IWHs. In one recent study examining IWHs with subclinical AF, the IWHs with AF developed DCM more commonly (50%) than control IWHs in sinus rhythm (21.1%) suggesting that subclinical AF in IWHs may be a precursor to DCM [39]. However not all IWHs with AF go on to develop DCM [25]. Reports suggest that between 80.5% and 87.6% of IWHs diagnosed with DCM are concurrently diagnosed with AF, likely due to the large mass of the atria [24, 25]. In this study, only one Deerhound was diagnosed with AF and this AFF hound had significant left atrial dilation. There were no Deerhounds without preclinical DCM or left atrial dilation diagnosed with subclinical AF, highlighting a breed difference. Explanations for this finding include perhaps Deerhounds being smaller in size compared to IWHs, therefore having a smaller atrial mass or due to differences in vagal tone between the two breeds. In this study, VAs were far more common than AF in AFF Deerhounds. This suggests that VAs in a clinically well Deerhound should not be ignored as it may be a sign of preclinical DCM and closer cardiac monitoring of the hound would be advisable. In addition, the presence of AF in a Deerhound may be an indicator of the presence of DCM with significant left heart dilation therefore an echocardiogram should be advised. Assessment of arrhythmias was not an aim of this study and further studies should be carried out to assess the relevance and breed RIs for supraventricular arrhythmias and VAs in this breed.

This study is not without its limitations. An important next step is to assess the accuracy of the proposed cut-off points in Tables 3 and 4 in the exact set of circumstances in which they are intended for use. Although EDV and ESV were indexed to BSA as this was in the original study design in 2014, it is no longer deemed mathematically correct to do so. It would be the subject for a future manuscript to describe the influence of BW on LV volumes. However, it is still valid to cite the ESVI and EDVI RI values for this single breed which have a relatively uniform BW. We did also plot BW values against BSA values and found excellent correlation (supplementary material). As many of the Deerhounds were examined at shows, it was not possible to weigh all of them on the same day as their ECHO examinations. They were weighed up to one week prior to their ECHO exams therefore some BW values may have been slightly inaccurate. All of the Deerhounds were scanned in the standing position. Although standing echocardiograms have been previously validated [9, 10], a separate validation study would be required to assess whether the RI in this study would apply to Deerhounds scanned in lateral recumbency. Although the European Society of Veterinary Cardiology have established published criteria for the early diagnosis of DCM [16], this points system is only a recommendation and has not been validated in individual dog breeds, other than Newfoundland dogs. Thyroid function was not assessed in all hounds therefore it was possible that some had undiagnosed hypothyroidism which may have altered the ECHO results. However, one study examining Doberman pinschers suggests that hypothyroidism does not seem to play a role in the aetiology or progression of DCM [12]. Not all hounds had Holter analyses therefore it was also possible that some VAs were missed and that some dogs were incorrectly classified. Assessing the usefulness of the ECHO variables using ROC analyses has its limitations when some of the variables, such as SPHI, LVDd and LVDs, were used as inclusion criteria. However, SPHI was still shown to be one of the least useful ECHO variables despite being part of the scoring system and an inclusion criterion. Finally, despite being a longitudinal study, with most hounds and their outcome being recorded by the principal investigator, it is possible that some NORM and EQUIV hounds may go on to develop DCM and that some EQUIV hounds may be reclassified as NORM following writing this paper.

Conclusions

In conclusion, not only does this study report new and revised RIs for Deerhounds, but it also highlights that Deerhounds have higher EDVI and ESVI than other breeds of dog. In view of the high prevalence of DCM reported in Deerhounds in this study, establishing echocardiographic RIs for this individual breed is important for screening purposes, as well as for early diagnosis therefore possibly treatment of DCM [26, 27]. VA could play an important part in Deerhounds affected with DCM.

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Figure 1.

Echocardiographic 2D images from a Deerhound showing end-diastolic (Figure 1a) and end-systolic (Figure 1b) volume measurements from the right parasternal 4-chamber long-axis view.

Figure 2.

Flowchart showing number of Deerhounds and their status, carried forward or reclassified following repeat echocardiograms. Shapes filled in red show number of Deerhounds which had repeat echocardiograms then changed group. Shapes filled in green show number of Deerhounds which had repeat echocardiograms but did not alter group category. Yellow shapes show the total number of Deerhounds in each group category following the final echocardiogram. For abbreviations, see Table 1.

Table 1. Statistical analysis of the differences between groups for ECHO and physical variables.

Variable	NORM (59)	EQUIV (10)	AFF (19)	Significance
Age at final ECHO (years) median (25%-75% interquartile range)	6.2 (5-8.2)	7.2 (5.5-9.6)	7.6 (5.9-9)	0.118
Weight (kg) (SD)	43.1 (7.5)	44.4 (5.4)	42.6 (6.0)	0.803
LVDd (mm) median (25%-75% interquartile range)	†53.7 (50.2-57.2)	†54.6 (50.6-57.8)	62.1 (58.6-66.2)	<0.001
LVDd (mm) Male (SD)	56.4 (4.675)	54.1 (5.058)	62.9 (4.638)	0.006
LVDd (mm) Female median (25%-75% interquartile range)	50.4 (49.4-54.4)	54.6 (51.1-58.2)	62.1 (58.6-65.4)	<0.001
LVDdn (SD)	† 1.77 (0.131)	† 1.78 (0.113)	2.1 (0.167)	<0.001
LVDs (mm) (SD)	† 39.2 (3.6)	† 41.6 (4.153)	51.5 (5.66)	<0.001
LVDs (mm) Male (SD)	40.4 (3.79)	42.1 (5.323)	51.1 (5.019)	<0.001
LVDs (mm) Female median (25%-75% interquartile range)	37.2 (36.0-40.0)	41.3 (38.9-42.2)	50.7 (47.7-54.8)	<0.001
LVDsn (SD)	† 1.19 (0.102)	† 1.26 (0.122)	1.55 (0.157)	<0.001
Simp EF % median (25%-75% interquartile range)	53.7 (49.4-58.1)	†42.4 (36.7-48.7)	†35.6 (34-38.9)	<0.001
FS % (SD)	26.8 (3.77)	23.4 (5.1)	17.8 (3.66)	<0.001
EDVI (mL/m^2) median (25%-75% interquartile range)	†112 (101.7-124.4)	†106.7 (99.6-128.4)	153 (140.7-169.7)	<0.001
ESVI (mL/m^2) median (25%-75% interquartile range)	50.5 (44.5-58)	†64.8 (57.4-79.8)	†99.2 (80.8-111.6)	<0.001
EPSS (cm) median (25%-75% interquartile range)	0.694 (0.629-0.776)	†0.911 (0.818-0.973)	†1.29 (1.04-1.569)	<0.001
SPHI (SD)	†† 1.588 (0.164)	††, † 1.526 (0.178)	† 1.425 (0.158)	<0.001
PEP:ET (SD)	† 0.466 (0.0854)	† 0.468 (0.132)	0.566 (0.103)	<0.001
LA:Ao median (25%-75% interquartile range)	†, †† 1.36 (1.28-1.42)	†† 1.295 (1.195-1.34)	† 1.42 (1.36-1.67)	0.009
LA l-axis median (25%-75% interquartile range)	† 49.3 (46-51.5)	†, †† 52.5 (48.7-58.7)	†† 53.0 (50.3-54.2)	0.001

EF: ejection fraction; EPSS: E point to septal separation; ESVI: end-systolic volume index; FS: fractional shortening; LA:Ao: left atrium to aorta ratio; LVDd: left ventricular M-mode internal dimension in diastole; LVDdn: left ventricular M-mode internal dimension in diastole after allometric scaling; LVDs: left ventricular M-mode internal dimension in systole; LVDsn: left ventricular M-mode internal dimension in systole after allometric scaling; PEP : ET: pre-ejection period to left ventricular ejection time ratio; SPHI: sphericity index; LA l-axis: left atrium diameter measured from the right parasternal long-axis view.

Table showing mean (standard deviation [SD]), unless otherwise stated for various ECHO and physical variables for healthy (NORM), equivocal (EQUIV) and affected (AFF) dogs.

†, †† Within each row, data that were not significantly different between the 2 indicated groups.

Echocardiographic Measurement	Number	^{A}Total range (minimum to maximum) in sample	^{B} 95% Reference intervals 2.5 – 97.5 Centiles (^{C} 90% CIs)	
			Lower	Upper
LVDd (mm) Male	27	44.30 – 63.11	47.08 (45.54-48.61)	65.78 (64.24-67.31)
LVDd (mm) Female	32	45.52 – 58.36	44.26 (43.19-45.32)	58.47 (57.41-59.54)
LVDdn	59	1.45 – 2.02	1.51 (1.49-1.53)	2.04 (2.01-2.06)
LVDs (mm) Male	27	30.60 – 47.31	32.80 (31.53-34.07)	48.26 (46.99-49.53)
LVDs (mm) Female	32	32.39 – 43.90	31.28 (30.26-32.30)	44.89 (43.87-45.91)
LVDsn	59	0.93 – 1.43	1.00 (0.97-1.02)	1.40 (1.38-1.43)
EDVI mLs/m^{2}	59	62.40 – 141.00	53.19 (16.02-66.71)	141.64 (139.16-144.03)
ESVI mLs/m^{2}	59	29.10 – 76.00	30.50 (28.30-32.71)	71.00 (68.80-73.21)
Simp EF %	59	40.06 – 70.40	40.39 (38.93-41.85)	67.28 (65.82-68.75)
FS %	59	19.20 – 35.20	18.79 (17.92-19.67)	34.87 (34.00-35.75)
PEP:ET	58	0.30 – 0.63	0.30 (0.28-0.31)	0.64 (0.62-0.66)
EPSS (cm)	59	0.47 – 0.99	0.48 (0.45-0.50)	0.93 (0.91-0.96)
LA:Ao	59	1.02 – 1.52	1.08 (1.04-1.11)	1.54 (1.52-1.56)
LA l-axis (mm)	59	34.40 – 62.40	39.24 (38.20-40.28)	58.31 (57.27-59.34)
SPHI	58	1.23 – 2.13	1.26 (1.23-1.30)	1.92 (1.88-1.95)

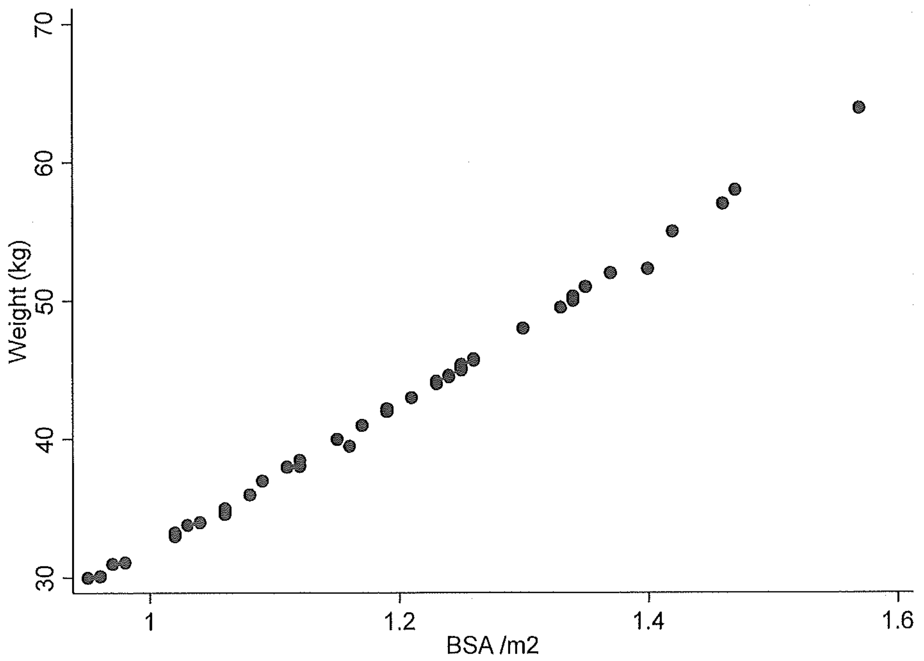
Table 2 Suggested reference intervals for ECHO parameters in healthy Deerhounds based on 95% estimate of 2.5th-97.5th percentile range of NORM Deerhounds. For abbreviations, see Table 1. ^{A}Total range (minimum – maximum) of values found in our sample ^{B} 95% Parametric reference range calculated as mean (+/- 2 standard deviations) ^{C} 90% Confidence Intervals (CIs) for upper and lower centiles.

Variable	AUC	Cut-off for Maximum Specificity	
		Optimal Cutoff	Sensitivity/Specificity (%)
Simp EF %	0.94	42.1	84.2 / 92.8
EDVI ml/m²	0.93	140.2	79.0 / 97.1
ESVI ml/m²	0.98	71.9	94.7 / 94.2
SPHI	0.75	1.53	79.0 / 61.8

Table 3 ROC Curve data for each ECHO variable when NORM/EQUIV dog are compared with AFF dogs. Values shown when specificity is maximised. For abbreviations, see Table 1.

			Cut-off for Maximum Specificity				Cut-off for Maximum Sensitivity			
	AUC		Optimal Cut-off		Sensitivity/ Specificity (%)		Optimal Cut-off		Sensitivity/ Specificity (%)	
Variable	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
LVDd (mm)	0.85	0.98	61.8	58	66.7/ 90.9	92.3/ 94.4	60.1	54.7	83.3/ 72.7	100.0/80.6
LVDs (mm)	0.97	0.99	45.6	45.1	100.0/ 90.9	92.3/ 100.0	45.6	42.5	100.0/ 90.9	100.0/88.9
	Male and Female				Male and Female				Male and Female	
LVDdn	0.92		1.98		73.7 / 95.7		1.83		94.7 / 63.8	
LVDsn	0.99		1.45		79.0 / 100.0		1.38		100.0 / 95.7	
FS %	0.95		21.1		84.2 / 91.3		22.0		94.7 / 85.5	
EPSS (cm)	0.98		1.0		84.2 / 98.6		0.84		100.0 / 76.8	
PEP:ET	0.78		0.61		52.9 / 91.2		0.41		94.1 / 25.0	
LA:Ao	0.7		1.42		57.9 / 76.8		1.13		100.0 / 0.10	

Table 4 ROC Curve data for each ECHO variable when NORM/EQUIV dog are compared with AFF dogs. Values shown when specificity and sensitivity are maximised respectively. For abbreviations, see Table 1.



Graph showing the high correlation between body weight and body surface area (BSA) in 59 healthy (NORM) Deerhounds. For the NORM dogs in this study, indexing to BSA is effectively identical to indexing to body weight.