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STANDARD ARTICLE

Comparison between real-time 3-dimensional and 2-dimensional biplane echocardiographic assessment of left atrial volumes in dogs with myxomatous mitral valve disease

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Background: Assessment of left atrial (LA) size is important in medical decision making and prognostication in dogs with myxomatous mitral valve disease (MMVD). Real-time 3-dimensional (RT3DE) and 2-dimensional echocardiographic (2DE) methods may be used to assess LA size.

Objectives: To compare measured LA volumes obtained by RT3DE with those calculated by biplane Simpson's modified method of discs (SMOD) and the area-length method (ALM) using the same RT3DE acquisition with the same timing.

Animals: One hundred twenty-one privately owned dogs with naturally occurring MMVD.

Methods: Prospective observational study comparing LA volumes indexed to body weight using RT3DE and 2DE-based biplane SMOD and ALM. Agreement between methods was evaluated using Bland-Altman plots and linear regression analyses.

Results: Estimations of LA volume using SMOD or ALM did not show good agreement with RT3DE-derived measurements. Absolute differences between methods increased with increasing LA volume, but SMOD underestimated whereas ALM overestimated calculated volumes compared to RT3DE-derived measurements. The difference in LA volume between RT3DE and the biplane methods showed a systematic underestimation of 7% for SMOD and a systematic overestimation of 24% for ALM. Comparison of LA volumes obtained by SMOD and ALM did not show good agreement. The ALM yielded 30% larger LA volumes compared to SMOD.

Conclusion and Clinical Importance: In comparison with RT3DE, SMOD systematically underestimated whereas ALM systematically overestimated LA volumes in dogs with MMVD. Because the systematic difference between RT3DE and SMOD was only 7%, SMOD might be considered the method of choice.

KEYWORDS
area-length method, canine, mitral regurgitation, Simpson's modified method of discs

Abbreviations: 2Ch, 2-chamber; 2DE, 2-dimensional echocardiography; 3DE, 3-dimensional echocardiography; 4Ch, 4-chamber; ALM, area-length method; Ao, aorta; BW, body weight; CHF, congestive heart failure; CV, coefficient of variation; IQR, interquartile range; LA, left atrium; LA/Ao, left atrial short-axis to aortic short-axis diameter ratio; LAlax/Ao, left atrial long-axis to aortic short-axis diameter ratio; LV, left ventricle; MMVD, myxomatous mitral valve disease; MR, mitral regurgitation; RT3DE, real-time 3-dimensional echocardiography; SMOD, Simpson's modified method of discs.

1 | INTRODUCTION

Left atrial (LA) size has been shown to be 1 of the strongest predictors of outcome in dogs with myxomatous mitral valve disease (MMVD).[1,2] Estimation of LA size is also important in decision making regarding medication in dogs with preclinical MMVD.[3] Mitral regurgitation (MR) causes increased LA preload which, in turn, causes LA dilatation.[4]

Because LA is a 3-dimensional structure, LA dilatation may occur in all directions (ie, cranio-caudal, medio-lateral, and ventro-dorsal) although perhaps not uniformly.[5,6] Traditionally, LA size is estimated using 1-dimensional or 2-dimensional echocardiographic (2DE) measurements of LA diameter or LA area, respectively.[7–10] Measurement of LA diameter commonly is estimated in the 2DE parasternal short-axis or long-axis view and indexed to aortic (Ao) diameter or body weight (BW) by use of allometric scaling.[7,11,12] Left atrial area measurements to derive LA volumes by use of monoplane or biplane Simpson's modified method of discs (SMOD) or the area-length method (ALM) recently have been recommended.[8–10,13] However, both algorithms are dependent on assumptions of a predefined geometrical elliptical or spherical form of LA. All 2DE-based measurements of LA depend on correct positioning and angulation of imaging planes. Therefore, the accuracy of 2DE-based diameter and area measurements in 1 or 2 planes to assess the size of 3-dimensional structures, such as the LA, may be questioned.

Volumetric scanning using real-time 3-dimensional echocardiography (RT3DE) has the advantage of independence of geometric modeling and image plane positioning, and thus the potential of providing more accurate estimates of chamber size.[14] The possible disadvantage with RT3DE is the use of ECG-gated stitching of 2, 4, or more datasets to create high spatial and high temporal resolution full volume 3D datasets. Stitching artifacts might occur as lines of disagreement between 2 neighboring subvolumes secondary to respiration or heart motion.[15] In people, RT3DE methods compare well with, whereas 2DE methods have been shown to systematically underestimate, gold standard volumetric methods, such as magnetic resonance imaging and multi-detector computed tomography, when estimating LA volumes.[16–19]

We previously have shown that indexed linear LA measurements or calculated volume approximations from 2DE-based dimensions of LA were not well correlated with RT3DE measurements of LA volume in dogs with MMVD, particularly at larger LA sizes.[14] However, biplane area 2DE methods might more accurately reflect LA volume, especially in enlarged hearts when dilatation might occur in >1 dimension. In a population of normal dogs, ALM correlated well with, whereas SMOD overestimated, LA volumes when compared to RT3DE-derived measurements.[20] Another study of dogs with and without MMVD comparing linear and 2DE-derived LA volumes showed that ALM yielded slightly larger volumes compared to SMOD, although the authors concluded that the 2 methods might be used interchangably.[8]

Although RT3DE might be expected to generate more accurate estimates of LA size compared to 2DE methods, it is currently more time-consuming, and off-line analysis using specialized equipment might be needed. In a clinical situation, where results of measurements are needed for immediate medical decision making, 2DE area measurements are sometimes used. This raises the question which of the 2 algorithms to estimate LA volume, SMOD or ALM, best agrees with RT3DE measurements of LA volumes in dogs affected by MMVD. Therefore, our aim was to compare measured LA volumes obtained by RT3DE with those calculated by SMOD and ALM using the same RT3DE acquisition with the exact same timing.

2 | MATERIALS AND METHODS

2.1 | Dogs

Privately owned dogs with MMVD presented to Albano Animal Hospital, Stockholm, Sweden, were included in the study. All dogs were evaluated according to the same protocol by physical examination, echocardiography, and, if needed, radiography, and using the same equipment. Dogs were included in the study based on diagnostic criteria for MMVD, including MV leaflets that were thickened or prolapsing or both and MR detected on color-coded Doppler echocardiograms.[11] Dogs with other acquired or congenital heart disease or systemic disease were excluded. Dogs were classified according to the American College of Veterinary Internal Medicine (ACVIM) classification of MMVD, in which dogs with LA-to-aortic ratios in parasternal right-sided short-axis view ≥1.6 were considered class B2 dogs, and all dogs with previous or present congestive heart failure (CHF) were considered class C dogs.[21] All examinations were performed and later evaluated by 1 veterinary specialist in cardiology (AT). The study was approved by the Ethical Committee for Animal welfare in Stockholm, Sweden, and informed owner consent was obtained before inclusion.

2.2 | 2DE and RT3DE

Two-dimensional and RT3D ECG-guided echocardiographic examinations were performed with an ultrasound unit (EPIQ; Philips Ultrasound, Bothell, WA) using 5.0-12 MHz phased-array transducers (for 2DE) and X5 or X7 MHz matrix transducers (for RT3DE) in all dogs. Dogs were unsedated and gently restrained in right and then left lateral recumbency during the examination. A complete echocardiographic examination was performed and measurements of LV diameters were made on 2DE-guided M-mode images obtained from parasternal right-sided short-axis views according to the American Society of Echocardiography.[22] Measurements of aorta (Ao) and LA in early ventricular diastole were made on the 2DE right parasternal short-axis view obtained at the level of the aortic valve in the first frame after aortic valve closure.[11] Measurements of LA also were made in the right parasternal long-axis view (LAlax) at ventricular end-systole timed as the frame preceding mitral valve opening. Both short-axis and long-axis LA dimensions were indexed to Ao diameter measured in short-axis view.[14] Measurements on M-mode images of LV and 2DE images of Ao and LA were made directly on the monitor freeze-frame image. For color flow investigation of MR, the Nyquist velocity limit was set at 0.6-0.7 m/s.[23] Continuous wave Doppler was used to measure MR velocities, and pulsed wave Doppler was used to measure aortic, pulmonic, and mitral E and A wave velocities.

The RT3DE images of the LA were obtained using the X5 or X7 matrix transducer (depending on the size of the dog) to obtain a pyramidal volume in real time. Transducer position was optimized to obtain apical 4-chamber (4Ch) and 2-chamber (2Ch) views of the LA.

2.3 | Data analyses

Off-line analyses of RT3DE volumes of LA were made using a software program (QLAB advanced quantification, version 10.8, Philips Ultrasound, Bothell, WA). Four smaller real-time volumes, acquired from 4 consecutive cardiac cycles, were combined to produce a larger pyramidal volume, providing a full-volume data set. Images with substantial stitching artifacts were not used in the analyses. Analysis of LA volume in LA end-diastole, concurrent with ventricular end-systole, was timed as the frame preceding mitral valve opening. The RT3DE image planes were optimized before reference points were placed. Four reference points (2 points in each view) placed at the endocardial border of the LA side of the mitral valve annulus in both 4Ch and 2Ch views were manually defined. A fifth reference point was placed at the midpoint of the dorsal LA border in either view. The endocardial border then was traced using an automated detection process to create a cast of the LA cavity. In the exact same 4Ch and 2Ch images, the algorithms for SMOD and ALM provided by the software (QLAB advanced quantification, version 10.8, Philips Ultrasound, Bothell, WA) and described elsewhere[24,25] were used to calculate LA volume (Figure 1).

2.3.1 | Variability

Within-day intra-observer variability was assessed using mean values and SD for each method and for each dog, in all dogs in which measurements could be analyzed 3 consecutive times without substantial stitching artifacts. To determine the coefficient of variation (CV), a mean measurement and SD were calculated for each dog and for each method, and the average CV for all dogs was reported for each method.

2.4 | Statistical analysis

A statistical program (JMP, v. 11.0, SAS Institute Inc, Cary, NC) was used for all statistical analyses and data are presented as total range, median, and interquartile range (IQR). Echocardiographic and Doppler variables in dogs with (Class C) and without (Class B) CHF according to the ACVIM classification were compared. The non-parametric Kruskal-Wallis test was used for testing equality of medians. The 3 methods (RT3DE, SMOD, and ALM) were compared by linear regression, comparing the fitted curves to the equality lines, and Bland-Altman plots, in which the mean bias and 95% confidence intervals were calculated. Level of significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Dogs

One-hundred twenty-one privately owned dogs of 43 breeds were included in the study: Cavalier King Charles spaniel (24), Miniature Schnauzer (13), Dachshund (10), mixed breed (7), Chinese Crested (5), Chihuahua (5), Jack Russell terrier (5), and <5 dogs of 36 other breeds. There were 72 (60%) males and 49 (40%) females. Age at presentation ranged from 5 to 16 years, with a median of 10.5 years (IQR, 8.6-11.8 years). Body weight ranged from 2.2 to 36.7 kg, with a median of 9 kg (IQR, 6.7-12.5 kg). According to the ACVIM classification of MMVD, 33 (27%) dogs were classified with CHF as class C (3 dogs with active CHF and 30 dogs stabilized by CHF medication) and 88 (73%) dogs without CHF as class B (75 dogs in stage B1 and 13 dogs in stage B2). Heart rate ranged from 72 to 222 beats/minute, with a median of 130 beats/minute (IQR, 120-146 beats/minute). Sinus rhythm was present in 119 dogs and atrial fibrillation in 2 dogs.

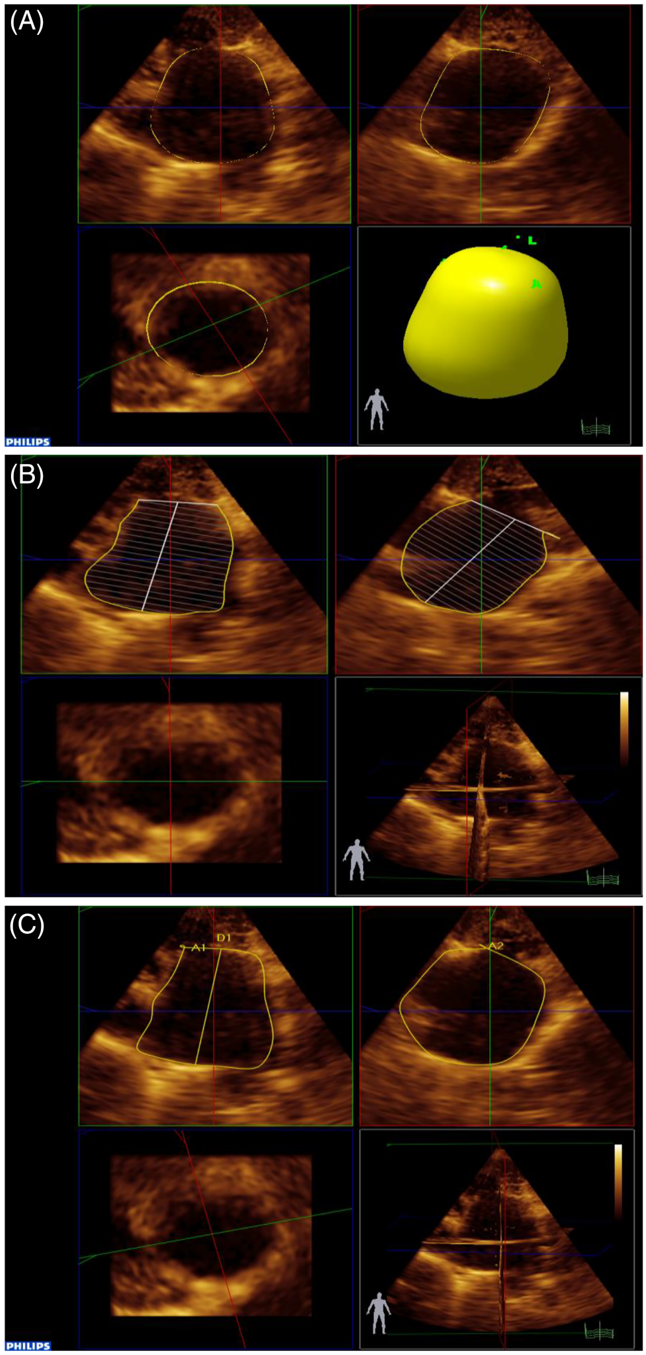

FIGURE 1 Left atrial (LA) volume measured using real-time 3-dimensional echocardiography (RT3DE) (A) and calculated LA volumes using Simpson's modified method of discs (SMOD) (B) and the area-length method (ALM) (C) in 121 dogs with myxomatous mitral valve disease

3.2 | 2DE and RT3DE

Baseline 2DE and RT3DE variables are presented in Table 1 with dogs classified according to ACVIM classification.

3.3 | Comparisons between 2DE biplane and RT3DE methods to estimate LA volume

The overall agreement between the biplane and RT3DE methods was reasonably good when compared to the equality lines (Figure 2A,D,G).

TABLE 1 Echocardiographic variables in 121 dogs with myxomatous mitral valve disease classified according to the ACVIM classification. Data are presented as median and IQR

Variable	Class B dogs (*n* = 88)	Class C dogs (*n* = 33)	*P* value
LA/Ao	1.15 (1.0-1.24)	2 (1.61-2.23)	<0.0001
LAlax/Ao	1.97 (1.72-2.24)	2.88 (2.47-3.27)	<0.0001
RT3DE LA volume/kg (mL/kg)	1.3 (0.84-1.64)	3.43 (2.69-4.4)	<0.0001
SMOD LA volume/kg (mL/kg)	1.15 (0.83-1.49)	3.18 (2.44-4.08)	<0.0001
ALM volume/kg (mL/kg)	1.5 (1.1-2.34)	4.23 (2.3-5.82)	<0.0001
Mitral E wave (cm)	0.68 (0.56-0.83)	1.05 (0.92-1.16)	<0.0001
Mitral A wave (cm)	0.68 (0.59-0.81)	0.73 (0.61-0.93)	0.15
E/A	1 (0.8-1.2)	1.2 (1-1.9)	0.001

Abbreviations: ALM, area-length method; Ao, aorta; IQR, interquartile range; LA, left atrium (short-axis view); LAlax left atrium (long-axis view); RT3DE, real-time 3-dimensional echocardiography, SMOD, Simpson's modified method of discs.

However, neither of the 2 biplane methods to estimate LA volumes corrected for MW showed complete agreement with the RT3DE-measured LA volume obtained from the same acquisition. The SMOD underestimated calculated LA volumes compared to RT3DE LA volumes, and absolute differences between methods increased with increasing size of LA (Figure 2B). The difference, expressed as a percentage of the mean volume, did not increase with increasing size of LA, but showed a systematic underestimation with a mean of 7% (Figure 2C). The ALM overestimated calculated LA volumes compared to measured RT3DE LA volumes, and absolute differences between methods increased with increasing size of LA (Figure 2E). The difference expressed as a percentage of the mean volume showed a systematic overestimation with a mean of 24% (Figure 2F). Comparison between ALM and SMOD to evaluate LA volume did not show good agreement between methods, and absolute differences increased with increasing size of LA (Figure 2H). Expressed as percentage of mean volume, ALM showed on average 30% higher values for LA volumes compared to SMOD (Figure 2I).

3.3.1 | Variability

Coefficient of variation was calculated in 78 of the 121 dogs in which 3 consecutive measurements could be obtained without substantial stitching artifacts and were considered to be good (<10%) to acceptable (<15%) for all 3 methods to estimate LA volumes, with the lowest CV values for RT3DE (median, 7%; IQR, 3-13%) followed by SMOD (median, 9%; IQR 5%-15%) and ALM (median, 10%; IQR, 6%-15%).

4 | DISCUSSION

Our study shows that none of the calculated LA volumes based on either of the 2 biplane methods showed good agreement with RT3DE volumes obtained from the same acquisition with the exact same timing in 121 dogs with MMVD. In comparison with RT3DE-derived LA volumes, SMOD systematically underestimated LA volumes by a mean of 7%, but the percentage difference between methods did not increase with increasing size of LA (Figure 2C). However, the absolute difference between methods increased with increasing LA volume (Figure 2B), which is in accordance with a study of humans in which SMOD underestimated RT3DE measurements of LA volumes and differences increased with increasing size of LA.[26] The ALM method overestimated LA volumes by a mean of 24%, but the percentage difference between methods did not increase with increasing size of LA (Figure 2F). The absolute difference between RT3DE and ALM increased with increasing LA volume in comparison with RT3DE (Figure 2E). The 2 2DE-based methods to assess LA volume should not be used interchangeably, because good agreement between SMOD and ALM was not found (Figure 2G-I).

Contrary to our findings, ALM showed good agreement whereas SMOD overestimated RT3DE-derived LA volumes in a population of normal dogs.[20] Because absolute differences increased between methods with increasing LA volumes in our study, this discrepancy might be explained by the fact that the previous study only included dogs without LA dilatation. Another study, evaluating absolute differences of LA volumes using ALM and SMOD in a large population of both normal dogs and dogs with MMVD showed good agreement between methods using Bland-Altman plots, suggesting that these 2 2DE-based methods can be used interchangeably.[8] One study evaluating ALM in dogs with and without MMVD showed that ALM yielded larger estimations of LA size in comparison with LA diameter indexed to aortic diameter, suggesting that ALM might be a superior method compared to the 1D method to detect LA dilatation.[10] Another explanation, based on findings in our study, however might be that ALM overestimates LA volumes. As neither study evaluated methods against a gold standard technique, the question regarding which method yields most accurate results remains unanswered.

Although not designed as a study for reference values of measured or calculated LA volumes, our findings appear comparable to those of previous studies concerning LA volumes indexed to BW. Previous studies using ALM have suggested an upper limit of 0.92[13] and 1.1 mL/kg[10] for LA volumes in normal dogs, respectively. In our study, median LA volumes for class B1 dogs were 1.2 mL/kg using RT3DE, 1.1 mL/kg using SMOD, and 1.5 mL/kg using ALM. Median LA volumes for class C dogs were 3.4 mL/kg using RT3DE, 3.2 mL/kg using SMOD, and 4.2 mL/kg using ALM (Table 1).

We used maximum LA volumes (ie, measured at ventricular end-systole) concurrent with atrial end-diastole for dogs in sinus rhythm, timed as the frame preceding mitral valve opening, to compare volumes derived from the 3 different echocardiographic methods. Most studies concerning LA volume support the use of maximal LA volume. However, mimimum LA volume, and not maximum LA volume, has been reported as a sensitive and specific measure to predict increased pulmonary wedge pressure,[27] and RT3DE minimum LA volume was the best independent predictor of major adverse cardiovascular events in people.[28] In a previous study, we did not find additional value of measuring minimum LA volumes in dogs with MMVD, because LA ejection fraction did not appear to be an independent marker of disease severity in dogs.[29]

Although it has been convincingly demonstrated that RT3DE measures LA volumes more accurately than do biplane 2DE methods in people in comparison with magnetic resonance imaging,[30] it is

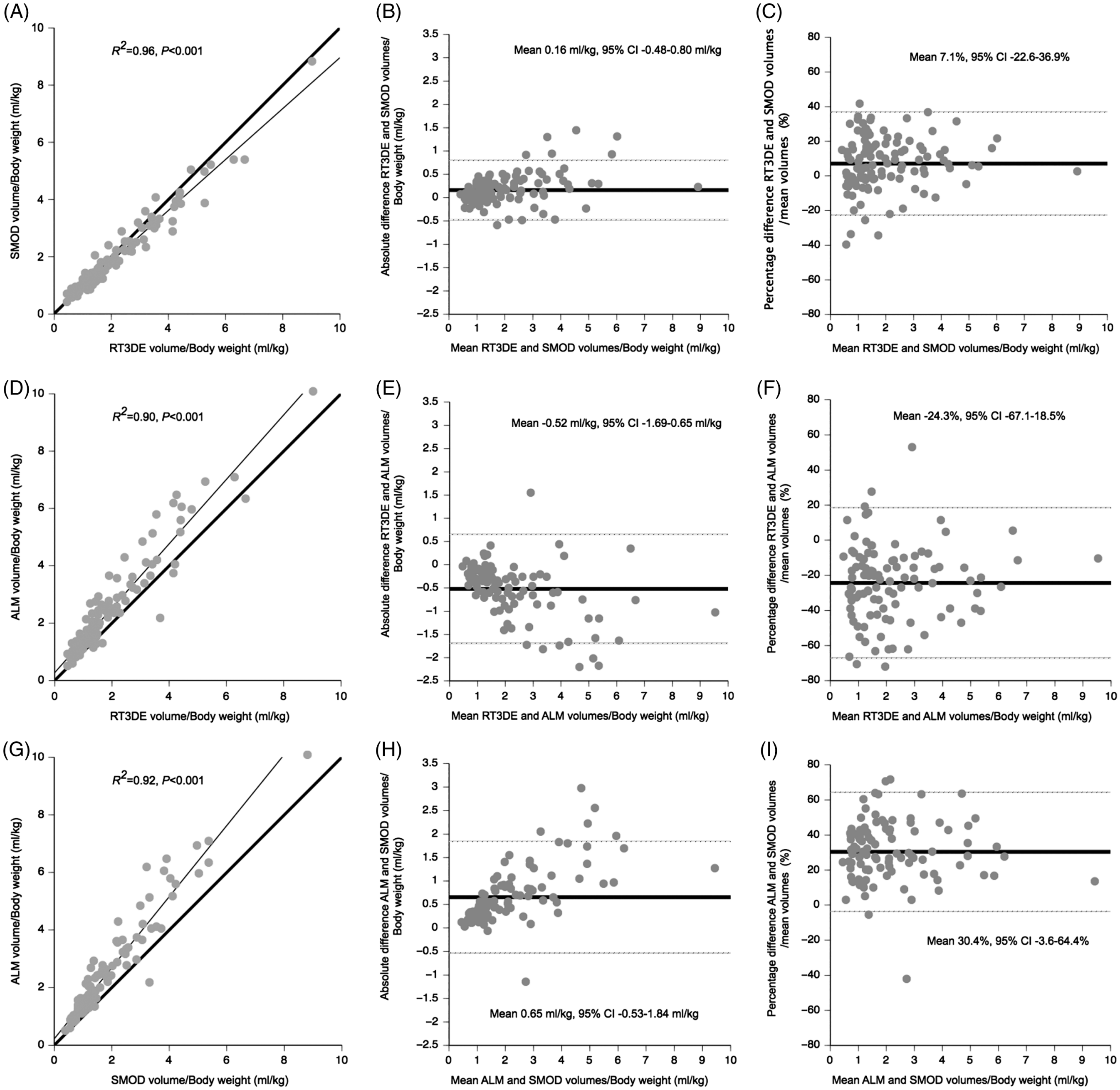

FIGURE 2 Regression lines (thin lines) between real-time 3-dimensional echocardiography (RT3DE), Simpson's modified method of discs (SMOD) and the area-length method (ALM) in 121 dogs (A, D, and G). Thick lines show complete agreement. Bland-Altman plots (B, C, E, F, H, and I) with mean and 95% confidence intervals of absolute differences (B, E, and H) and differences expressed as percentage of the mean volume (C, F, and I)

unclear whether or not this is true in dogs with MMVD. It is also pertinent to ask whether or not this potential incremental benefit of RT3DE measurements of LA is clinically important and if it has the potential to improve the prediction of outcome in dogs with MMVD. Longitudinal studies concerning prognostic indicators, including RT3DE measurements in dogs with MMVD, are needed to answer this question.

4.1 | Limitations

Because RT3DE measurements of LA volume were not evaluated against a gold standard technique, such as magnetic resonance imaging and multi-detector computed tomography, RT3DE could not be evaluated for accuracy regarding the true volume of LA in dogs with MMVD. In our study, all measurements were made in the exact same acquisition in each dog, which is considered an advantage in a comparative study. However, results from our study might not be applicable to other dogs, where measurements are made on 2DE images, because then comparisons are made between images obtained at different times and possibly at different locations.

In conclusion, neither of the 2 biplane estimations of LA volumes corrected for BW using SMOD or ALM showed good agreement with RT3DE-generated LA volumes obtained from the same acquisition. The absolute differences between methods increased with increasing size of LA, but the percentage differences were reasonably constant over the range of LA sizes of dogs included in the study. The systematic difference of 7% between RT3DE and SMOD probably is of little consequence in the clinical setting, whereas the 24% difference between RT3DE and ALM and the 30% difference between SMOD and ALM presumably are of more clinical importance. The 2 2DE-based methods should not be used interchangeably because good agreement between methods was not found.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the Ethical Committee for Animal Welfare in Stockholm, Sweden.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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