Radial and Longitudinal Strain and Strain Rate Assessed by Speckle-Tracking Echocardiography in Dogs with Myxomatous Mitral Valve Disease

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Background: Assessment of left ventricular (LV) function using conventional echocardiographic methods is difficult in mitral regurgitation (MR) owing to altered hemodynamic loading conditions. Newer methods such as speckle-tracking echocardiography (STE) provide assessment of LV strain (St) and strain rates (SR).

Hypotheses: Global St and SR are 1) decreased in dogs with clinical signs of congestive heart failure (CHF) due to myxomatous mitral valve disease (MMVD) compared with clinically healthy dogs, and are 2) associated with conventional echocardiographic indices of MMVD severity.

Animals: The study subjects were 93 privately owned dogs with different MMVD severities.

Methods: Prospectively recruited dogs were grouped according to MMVD severity based on echocardiographic evaluation of MR and presence of clinical signs. Global radial and longitudinal St, SR, and indices of LV dyssynchrony were assessed.

Results: On group-wise comparisons, dogs with CHF had increased global longitudinal St, global longitudinal and radial SR in systole (SRs), and early diastole (SRe) compared with dogs with no or minimal MR (all $P < .04$). On multiple regression analyses, these global STE variables increased with degree of MR, but associations with left atrial-to-aortic root ratio (LA/Ao) were best described by second-order polynomial equations. Thus, curvilinear relationships were found for LA/Ao and longitudinal St, SRs, and SRe (all $P < .002$) and radial St and SRe (all $P < .001$).

Conclusions and Clinical Importance: Assessed by STE, LV function appeared to be augmented in moderate-to-severe disease. However, at CHF stages with greatly enlarged atria, a decrease to levels comparable to dogs with no or minimal MR was observed.

Key words: Deformation; Deformation Rate; Mitral regurgitation; Ventricular function.

Myxomatous mitral valve disease (MMVD) is considered primarily a valvular disease,[1] although myocardial changes, including fibrosis and arterial narrowing, have been reported in dogs with congestive heart failure (CHF) due to MMVD.[2] Although myocardial dysfunction has not been regarded a predominant feature in dogs with MMVD[3] and the global pump

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Abbreviations:

4-Ch	left apical 4-chamber
ANT	anterior myocardial segment
AntSept	anteroseptal myocardial segment
ApLat	apical-lateral myocardial segment
ApSept	apical-septal myocardial segment
ARJ/LAA	area of regurgitant jet/left atrial area
AVC	aortic valve closure
BasLat	basal-lateral myocardial segment
BasSept	basal-septal myocardial segment
BW	body weight
CHF	congestive heart failure
CKCS	Cavalier King Charles Spaniel
E′	peak early diastolic velocity of the septal mitral annulus
E	peak early diastolic mitral inflow velocity
FR	frame rate
FS	fractional shortening
HR	heart rate
Inf	inferior myocardial segment
LA/Ao	left atrial-to-aortic root ratio
Lat	lateral myocardial segment
LSRa	global longitudinal strain rate in late diastole
LSRe	global longitudinal strain rate in early diastole
LSRs	global longitudinal strain rate in systole
LSt	global longitudinal systolic strain
LVIDd$_{inc}$	percentage increase from expected normal in left ventricular internal diameter in diastole
LVIDd	left ventricular internal diameter in diastole
LVIDs$_{inc}$	percentage increase from expected normal in left ventricular internal diameter in systole
LVIDs	left ventricular internal diameter in systole
LV	left ventricular
MidLat	mid-lateral myocardial segment
MidSept	mid-septal myocardial segment

MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
PHT	pulmonary hypertension
Post	posterior myocardial segment
ROI	region of interest
RSRa	global radial strain rate in late diastole
RSRe	global radial strain rate in early diastole
RSRs	global radial strain rate in systole
RSt	global radial systolic strain
SAX	parasternal short axis view at the level of the papillary muscles
SDI	standard deviation of the regional timing of peak radial strain
SD	standard deviation
Sept	septal myocardial segment
SRa	peak late diastolic strain rate
SRe	peak early diastolic strain rate
SRs	peak systolic strain rate
SR	strain rate
STE	speckle-tracking echocardiography
STI	synchrony time index
St	peak systolic strain

function apparently is maintained for a long period of time, many dogs eventually develop CHF. The pathogenesis is not yet fully understood. Myocardial dysfunction already present at early stages of the disease may be masked by favorable loading conditions as a decreased load-independent contractile reserve has been observed in dogs with experimental chronic MMVD before the onset of CHF.[4,5] Conventional echocardiographic indicators of left ventricular (LV) function such as fractional shortening (FS) and end-systolic LV dimensions are highly influenced by the change in hemodynamic load associated with the presence of MR, although end-systolic LV dimensions are affected to a lesser extent than FS.[3,6] Therefore, newer methods have been developed for the quantification of LV function. One of these methods is speckle-tracking echocardiography (STE), a technique that allows studies of myocardial deformation. The magnitude of deformation is described by systolic strain (St), defining the myocardial deformation during systole relative to the initial length or thickness at the onset of the cardiac cycle, whereas the rate of deformation is described by strain rate (SR). The STE technique is based on tracking of speckles, representing specific distributions of ultrasound reflections from the myocardium, in the 2-dimensional echocardiogram. Segmental radial and longitudinal St and SR have shown good correlation with invasive indices of LV function, assessed as maximal rate of LV pressure increase,[7] and good accuracy compared with sonomicrometry in dogs.[8] Using STE in healthy awake dogs, good reproducibility was found for radial and longitudinal St and radial SRs averaged over segments,[9,10] whereas lower reproducibility of longitudinal SR was reported, especially for the average of segments constituting the LV free wall.[10]

The overall aim of this study was to examine the global radial and longitudinal STE-derived St and SR

in the left ventricle of dogs with increasing MMVD severity. Because the likelihood of developing MMVD differs among breeds, both clinically healthy Cavalier King Charles Spaniels (CKCS), being highly predisposed, and Beagles, having a lower predisposition,[11] were included in the study. Specifically, the aims were: (1) to compare global St and SR in dogs with clinical signs of CHF due to MR caused by MMVD to dogs with no or minimal and compensated MR, (2) to examine whether global St and SR differed between dog groups with no or minimal MR, but with a different predisposition to MMVD or differed between CKCS and dogs of other breeds with clinical signs of CHF, and finally (3) to examine possible associations between global St and SR and conventional echocardiographic indices of MR severity and LV remodeling.

Materials and Methods

Recruitment and Conventional Echocardiographic Examination of Dogs

The prospective observational study included 97 privately owned dogs $\geq$ 4 years of age. Exclusion criteria encompassed pregnancy, lactation, and clinical systemic or organ-related disease, apart from heart disease caused by MMVD, determined by clinical and echocardiographic examinations and evaluation of CBC and serum biochemistry results. Furthermore, presence of systemical hypertension, defined by noninvasively measured systolic blood pressure > 175 mmHg, led to exclusion. Dogs with clinical signs of CHF were allowed cardiac treatment, whereas the remaining dogs did not receive any medication.

Dogs were divided into 6 MMVD severity groups based on the degree of MR (described by the maximal area of the regurgitant jet during systole estimated in percentage of the left atrial area, ARJ/LAA),[12,13] breed, and the presence of clinical signs of CHF: (1) Beagles with no or minimal MR (ARJ/LAA $\leq$ 15%); (2) CKCS with no or minimal MR; (3) CKCS with mild MR (20% $\leq$ ARJ/LAA $\leq$ 50%); (4) CKCS with moderate or severe MR (ARJ/LAA > 55%) but no clinical signs of CHF; (5) CKCS and (6) dogs of different breeds with moderate or severe MR, LA/Ao $\geq$ 1.7 and clinical signs of CHF due to MR attributable to MMVD. Clinical signs of CHF were defined as a history of cough, dyspnea, and exercise intolerance responsive to furosemide treatment, indicating presence of pulmonary edema. Dogs were examined after confirmed effect of furosemide, which consisted of alleviation or complete normalization of respiratory effort and rate. However, dogs did not necessarily have to be stable on medication on the day of STE examination. The dogs were recruited from the Department of Veterinary Clinical and Animal Sciences, University of Copenhagen, Denmark, the veterinary cardiology referral practice Din Veterinär, Sweden, and the animal hospital Blå Stjärnan, Sweden. All owners gave their consent, and the study was approved by the Danish Animal Welfare Division and the Local Ethical Committee in Gothenburg, Sweden.

The examination comprised owner interview, blood sampling, clinical and echocardiographic examination, performed without sedation in left and right lateral recumbency. The echocardiography was performed using a Vivid *i* echocardiograph[a] with continuous ECG. The percentage ARJ/LAA was estimated semi-quantitatively to the nearest 5% from the left apical 4-chamber (4-Ch) and the right parasternal long axis views by color flow mapping.[12] Left atrial-to-aortic root ratio (LA/Ao) was evaluated from a 2-dimensional short axis view[14] and tricuspid and pulmonary valve

competence and regurgitation velocities were evaluated in the 4-Ch and the parasternal short axis views, respectively. The LV dimensions, presented here as the percentage increase from the calculated expected dimensions,[15] were measured from the short axis view and were used for the calculation of FS. From the 4-Ch view, the peak early diastolic mitral inflow velocity (E), measured using pulsed Doppler, and the peak early diastolic velocity of the septal mitral annulus (E′), measured using pulsed tissue Doppler, were used for the calculation of E/E′.[16] All echocardiographic examinations and offline measurements of conventional echocardiographic variables were performed on separate days using image software[b] by 1 experienced operator (LHO) blinded to the identity of each dog.

Speckle-Tracking Echocardiography

During the echocardiographic examination, 2-dimensional digital cine loops with a minimum of 9 cardiac cycles were acquired using a frame rate (FR) of 64–100 per second in the right parasternal short axis view at the level of the papillary muscles (SAX) and in the left apical 4-Ch view, respectively. Postprocessing was performed by 1 observer (NEZ), who was blinded to the identity of the dog and also to the results of the conventional echocardiographic examinations. As previously described,[9,10] the endocardial border was manually defined, and an automatic frame-by-frame tracking of speckle patterns was performed. The software used[b] automatically divided the ventricle into 6 segments in accordance with standard segmentation models used in humans (Fig 1). A manual adjustment of the region of interest (ROI) and a visual inspection at decreased playback speed were performed. Segments marked by the software as being of inadequate tracking quality were excluded and complemented by manual exclusion of segments if the ROI did not follow the myocardium properly throughout the entire cardiac cycle, thus overruling the tracking score assigned by the software. Peak values were manually corrected when necessary. Only cardiac cycles with ≥ 4 segments of adequate tracking quality and with no signs of arrhythmia, aside from respiratory sinus arrhythmia, were included. Peak systolic St and peak systolic SR (SRs) were defined as the maximal deflections of the respective curves during the ejection phase, defined from the ECG. Similarly, peak early (SRe) and late (SRa) diastolic SR were defined as the maximal curve deflections during early and late diastolic phases, respectively, also determined by use of the ECG (Fig 1). Segmental St and SR values plus the time from peak of R wave to peak systolic radial St were automatically calculated and transferred to a spreadsheet. In cases where fusion of the SRe and SRa waves occurred, both values were excluded. From the SAX view, segmental values were averaged to obtain global radial systolic St (RSt), global SR in systole (RSRs) as well as early (RSRe) and late (RSRa) diastole. Similarly, segmental values from the 4-Ch view were averaged to obtain global longitudinal systolic St (LSt), global SR in systole (LSRs) as well as early (LSRe) and late (LSRa) diastole. As previously described, segmental dyssynchrony was calculated as the difference in timing of the peak radial St from the earliest to the latest segment, the synchrony time index (STI),[9] and the standard deviation (SD) of the timing of segmental peak radial St (SDI).[17] All measurements were averaged from 3 heart cycles.

To assess the repeatability of the STE analyses, interexamination variability was evaluated by repeated echocardiographic examination of 6 dogs (3 clinically healthy CKCS and 3 CKCS with clinical signs of CHF) at 6 different time points on the same day. Images from each of the 6 examinations were postprocessed by 1 observer (NEZ). Furthermore, the intraobserver between-day variability was evaluated by repeated (6 times) postprocessing of 1 examination from each of the above-mentioned 6 dogs.

Statistical Analysis

Statistical analyses were performed using statistical software.[c] Logarithmic transformations were used, when appropriate, to achieve normality and homogeneity of the residuals. Overall group-wise differences in descriptive data, conventional echocardiographic indices, and STE-derived variables were investigated using analysis of variance and posthoc tests with a Tukey-Kramer-adjusted P value for multiple testing.

Furthermore, least squares multiple linear regression analyses were performed with the measured STE-derived variables as outcome and separately entered predictors, including percentage ARJ/LAA, LA/Ao, percentage increase in LV internal diameter in systole (LVIDs$_{inc}$) and in diastole (LVIDd$_{inc}$), FS, and E/E′. Age, sex, body weight (BW), heart rate (HR; calculated from the ECG during the 3 cardiac cycles used for postprocessing), presence of pulmonary hypertension (PHT, defined as tricuspid regurgitation velocity > 2.8 m/s or pulmonary regurgitation velocity > 2.2 m/s),[18] and CKCS (yes/no) were included as covariates in all models. Numerical values of STE variables were used for statistical analyses. No interactions were included; however, a second-order polynomial for each of the predictors was included in the respective model, because the association between the explanatory variables and outcome variables seemed visually to fit best with a second-degree polynomial function. Reductions were performed in a backward, stepwise manner until only statistically significant effects remained. If both the predictor itself and its squared derivative were left in the final model, the vertex of the parabola was calculated from the estimates of the final model $f(x) = ax^2 + bx + c$ as: $x = (-b)/2a$. Because each of the 6 explanatory variables was entered separately, the significance level in multiple regression analyses was corrected to $P = .008$.

For the repeatability study, the mean and SD values resulting from postprocessing of repeated examinations of dogs and repeated postprocessing of the same examination from each dog were used for the calculation of interexamination and between-day coefficients of variation (CV), respectively. The interexamination variability for all variables moreover was tested by the following ANOVA model with random effects:

$$Y_i = \mu + a(\text{exam}_i) + b(\text{CHF}_i) + c(\text{dog}_i) + \epsilon_i$$

Where $c(1),..,c(6)$ were random intercepts for the 6 dogs; μ was the general mean; a was the fixed effect of exam (1–6); b was the fixed effect of presence of clinical signs of CHF (yes/no) and ϵ_i was the model error, representing variation due to differences in image acquisition, HR, and postprocessing. The contribution of the model error to total variation was calculated as: $\sigma^2/(\sigma^2_{\text{dog}} + \sigma^2)$ for each variable.

Results

Two dogs were excluded due to signs of systemic disease and lack of furosemide responsiveness, respectively, and 2 dogs had > 2 segments of inadequate tracking quality in both the 4-Ch and the SAX views. During the examination of 1 Beagle, a FR < 60 was used in the SAX view. Therefore, 1 dog contributed only to the calculation of longitudinal deformation. Thus, a total of 93 dogs (45 females and 48 males) with a mean age of 7.5 years (±3.0) were included in the study (Table 1). A total of 65 CKCS, 14 Beagles, 5 Dachshunds, and 3 Jack Russell Terriers were included, whereas King Charles Spaniel, Cocker Spaniel, Bichon Frise, Maltese, Boston Terrier, and mongrel dog each were represented by 1 individual.
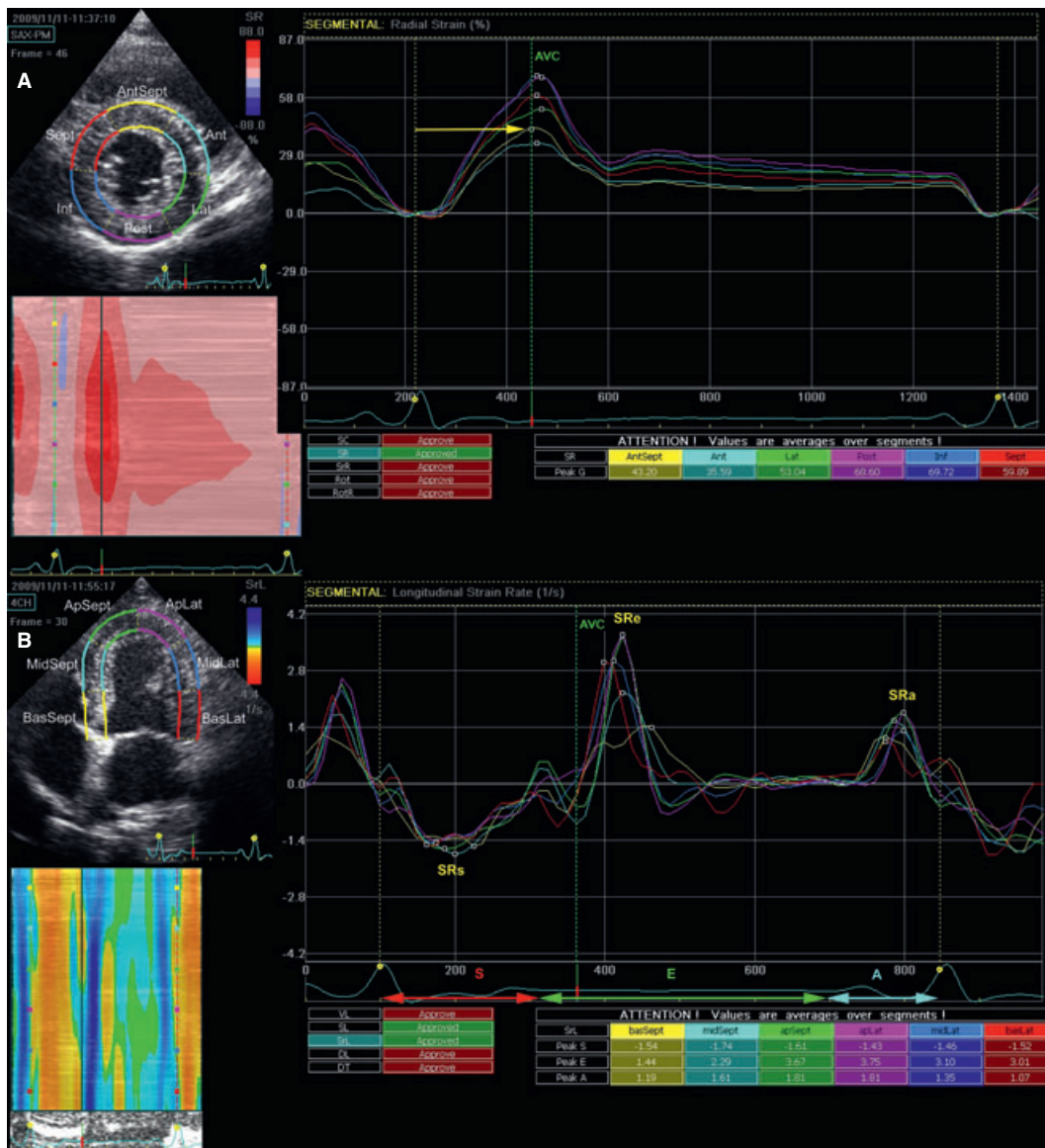
Fig 1. Example of (A) radial strain (St) and (B) longitudinal strain rates (SR) in a Cavalier King Charles Spaniel with mild mitral regurgitation. According to human anatomy classification, the myocardium was automatically divided into 6 segments: anteroseptal (AntSept), anterior (Ant), lateral (Lat), posterior (Post), inferior (Inf), septal (Sept) in the short axis view (A) and: basal-septal (BasSept), midseptal (MidSept), apical-septal (ApSept), apical-lateral (ApLat), midlateral (MidLat), and basal-lateral (BasLat) in the apical 4-chamber view (B). Radial St is positive in systole representing a thickening of the myocardium, whereas the longitudinal systolic St, and thus systolic SR (SRs), are negative, representing a shortening. During relaxation, the myocardium lengthens, represented by the positive early (SRe) and late (SRa) longitudinal diastolic SR waves. The time from peak of R wave to peak radial St is illustrated for the AntSept segment (arrow). The timing of systole (S), early (E) and late (A) diastole were assessed from the ECG, as shown with labeling. The automatically calculated timing of aortic valve closure (AVC) was based on the weighted average of time to peak St of all accepted segments. Peak segmental St was, however, often encountered after this AVC as illustrated. Therefore, the automatically calculated AVC was not used for timing purposes, and the maximum deflection of the St curve during ejection phase was used as regional peak systolic St.

Dogs with clinical signs of CHF were treated with individual combinations of furosemide (31), pimobendan (23), benazepril (23), spironolactone (8), digoxin (5), and propranolol (3). Presence of PHT was found in 21 dogs, primarily in dogs with moderate or severe MR. The LSt and the RSt could be obtained in 85 and 92 dogs, respectively, using a mean FR of 86 ± 7. Remaining dogs had < 4 segments of acceptable tracking quality in 1 or more cardiac cycles. Tracking of 3 consecutive cardiac cycles was not feasible in either the 4-Ch or the SAX views in 13 dogs, thus 2 consecutive cycles and 1 cycle in proximity were analyzed. Of the 85 dogs contributing to the calculation of LSt variables, all 6 segments in each of 3 cardiac cycles were of adequate tracking quality in 36 dogs, whereas the remaining 49 dogs had either 1 or 2 myocardial segments of inadequate quality in at least 1 cycle. Of a total of 1530 segments (6 segments analyzed in each

Table 1. Characteristics of the 93 included dogs.

	Beagle, No/ Minimal MR	CKCS, No/ Minimal MR	CKCS, Mild MR	CKCS, Moderate/ Severe MR	CKCS, CHF	Different Breeds, CHF
n	14	17	14	17	17	14
ARJ/LAA (%)[*]	0 (0–5)	5 (5–10)	25 (20–40)	80 (70–100)	100 (100–100)	100 (100–100)
Gender (m/f)	7/7	6/11	5/9	11/6	10/7	10/4
Age (years)	6.4 ± 2.0	5.4 ± 1.2[1]	5.6 ± 1.4	7.1 ± 1.6[2]	10.2 ± 2.2[1,2,3,4]	12.1 ± 1.6[1,2,3,4]
Body weight (kg)	13.9 ± 1.4	9.7 ± 1.7[1]	9.5 ± 1.7[1]	10.0 ± 1.6[1]	10.4 ± 1.7[1]	10.1 ± 3.6[1]
LA/Ao (ratio)	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.6 ± 0.2[1,2]	2.1 ± 0.4[1,2,3,4]	2.2 ± 0.5[1,2,3,4]
LVIDd (cm)	3.5 ± 0.4	2.9 ± 0.2[1]	3.0 ± 0.4[1]	3.3 ± 0.4	4.3 ± 0.6[1,2,3,4]	4.1 ± 0.6[1,2,3,4]
$LVIDd_{inc}$ (%)	6.1 ± 12.8	−1.1 ± 6.2	0.5 ± 12.2	9.4 ± 15.4	40.9 ± 19.3[1,2,3,4]	37.2 ± 9.3[1,2,3,4]
LVIDs (cm)	2.5 ± 0.2	2.1 ± 0.2[1]	2.1 ± 0.3	2.2 ± 0.3	2.5 ± 0.5	2.5 ± 0.6[2]
$LVIDs_{inc}$ (%)	16.5 ± 10.0	7.8 ± 10.9	11.3 ± 12.3	13.7 ± 14.4	24.1 ± 23.3[2,3]	29.8 ± 20.0[2,3,4]
FS (%)	27.3 ± 7.6	28.9 ± 6.9	27.6 ± 8.0	31.8 ± 7.7	42.8 ± 4.5[1,2,3,4]	38.4 ± 8.5[1,2,3]
E (m/s)	0.7 ± 0.2	0.7 ± 0.1	0.8 ± 0.1	1.0 ± 0.2[1,2]	1.4 ± 0.3[1,2,3,4]	1.6 ± 0.3[1,2,3,4]
E/E′ (ratio)	10.6 ± 2.8	10.6 ± 2.3	11.7 ± 1.5	13.4 ± 4.1[1]	12.6 ± 3.2[1]	14.2 ± 5.6[1]
TR (n)	0	5	6	11	14	11
TRV (m/s)	–	2.3	2.7	2.5	3.2	3.1

Within each row, superscripts [1,2,3,4] indicate a value being statistically significantly different from Beagles with no/minimal mitral regurgitation (MR), Cavalier King Charles Spaniels (CKCS) with no/minimal MR, mild MR, and moderate/severe MR, respectively (all Tukey-Kramer-adjusted $P < .05$). All values except ARJ/LAA are reported as mean and standard deviation.

CHF, clinical signs of congestive heart failure due to MR attributable to myxomatous mitral valve disease; E/E′, peak early diastolic mitral inflow velocity divided by peak early diastolic velocity of the septal mitral annulus; FS, fractional shortening; LA/Ao, left atrial-to-aortic root ratio; LVIDd, left ventricular internal diameter in diastole; $LVIDd_{inc}$, percentage increase in LVIDd; LVIDs, left ventricular internal dimensions in systole; $LVIDs_{inc}$, percentage increase in LVIDs. TRV: average peak tricuspid regurgitation velocity in dogs with presence of tricuspid regurgitation (TR).

*Reported as median and interquartile range.

of 3 cycles in 85 dogs), 126 (8.2%) segments were of inadequate tracking quality in the 4-ch view. Of the 92 dogs contributing to RSt variables, all 6 segments in the 3 cycles were of acceptable tracking quality in 74 dogs. Of a total of 1656 segments (6 segments analyzed in each of 3 cycles in 92 dogs), 74 (4.5%) segments were of inadequate tracking quality in the SAX view. The most commonly excluded segment was the basal-lateral segment in the 4-Ch view, comprising almost

50% of excluded segments. Manual exclusion constituted 13.3% of all excluded segments.

Repeatability

Repeatability is summarized in Table 2. Two dogs with clinical signs of CHF did not fully contribute to the calculation of variability of LSt and derived SR, because the 4-Ch view could not be tracked in

Table 2. Intraobserver repeatability of global strain and strain rates in 6 dogs[*] assessed by between-day variability (of same examination) and interexamination variability (6 different examinations of each dog).

	Between-Day SD	Between-Day CV (%) (range)	Interexamination SD	Interexamination CV (%) (range)
LSt (%)	0.91	4.7 (3.3–7.6)	1.4	7.1 (3.1–15.6)
LSRs (s^{-1})	0.04	4.2 (2.7–7.8)	0.09	9.2 (3.7–17.0)
LSRe (s^{-1})	0.18	7.4 (2.9–7.8)	0.22	8.4 (6.5–10.0)
LSRa (s^{-1})	0.09	4.6 (3.2–8.7)	0.24	12.3 (6.2–22.3)
RSt (%)	5.3	8.6 (1.1–14.3)	4.8	8.0 (4.9–13.3)
RSRs (s^{-1})	0.19	5.4 (1.6–8.7)	0.30	8.8 (7.7–11.6)
RSRe (s^{-1})	0.29	8.9 (2.8–14.8)	0.46	14.2 (3.9–26.2)
RSRa (s^{-1})	0.30	12.7 (6.5–18.7)	0.45	18.3 (16.0–20.3)
STI (ms)	8.9	21.0 (11.1–37.7)	20.3	49.0 (18.5–102.0)
SDI (ms)	3.4	18.0 (7.0–33.1)	7.8	37.6 (18.8–79.3)

*Two dogs with clinical signs of congestive heart failure did not contribute fully due to inadequate tracking quality of the apical 4-chamber view in 2/6 and 6/6 examinations, respectively.

CV, coefficient of variation; LSRa, global longitudinal strain rate in late diastole (SRa); LSRe, global longitudinal strain rate in early diastole (SRe); LSRs, global longitudinal strain rate in systole (SRs); LSt, global longitudinal systolic strain (St); MR, mitral regurgitation; RSRa, global radial SRa; RSRe, global radial SRe; RSRs, global radial SRs; RSt, global radial St; SD, standard deviation; SDI, standard deviation of the regional timing of peak radial strain; STI, difference in timing of the peak radial strain from the earliest to the latest segment.

adequate quality in any, or only in 4/6, examinations, respectively. No effect of examination number was found for any STE-derived variable, whereas a significant effect of presence of clinical signs of CHF was found for LSt, LSRe, and RSRs. The model error was proportionally higher in dogs with clinical signs of CHF than in clinically healthy dogs for these latter variables. The lowest contribution from model error to total variation was found for LSRs (24.1%), whereas the highest was found for STI (92.2%).

Group-Wise Comparisons

Global longitudinal St, LSRs, LSRe, RSRs, and RSRe all were increased in either 1 or both dog groups with clinical signs of CHF, compared with either 1 or both groups with no or minimal MR (Tables 3 and 4). No global St or SR variable differed between dogs with compensated moderate or severe MR and dogs with clinical signs of CHF. Similarly, no global St or SR variable differed between Beagles and CKCS with

no or minimal MR, or between CKCS and other breeds with clinical signs of CHF.

Multiple Regression Analyses

In the multiple regression analyses, LSt, RSt, LSRs, RSRs, LSRe, and RSRe all increased linearly with percentage ARJ/LAA (all $P < .003$) (Table 5). However, in the multiple regression analyses with LA/Ao, the associations with LSt, RSt, LSRs, LSRe, RSRe, and LSRa were best described using second-degree polynomial equations (Table 5). The vertices of the resultant parabolas ranged from LA/Ao of 2.0 to 2.3 (Fig 2). Heart rate was a significant covariate in models predicting LSRs and RSRs and had the highest model R^2. Significant positive associations were found for FS and several variables: LSt and RSt (both $P < .0001$), LSRs and RSRs (both $P < .0001$; covariation with HR), LSRe ($P < .0001$) and LSRa ($P = .005$, covariation with BW). The highest adjusted R^2 (0.54) was found for the association between FS, HR, and LSRs

Table 3. Global longitudinal strain and strain rates evaluated from the apical 4-chamber view.

	Beagle, No/ Minimal MR	CKCS, No/ Minimal MR	CKCS, Mild MR	CKCS, Moderate/ Severe MR	CKCS, CHF	Different Breeds, CHF
n	12	16	13	16	15	13
HR (min^{-1})	98 ± 36	117 ± 25	117 ± 17	126 ± 28	135 ± 19[1]	128 ± 34[1]
LSt (%)	−18.8 ± 1.1	−18.2 ± 2.4	−19.6 ± 3.2	−22.5 ± 2.4[2]	−23.9 ± 2.7[1,2,3]	−21.8 ± 4.5[2]
LSRs (s^{-1})	−2.0 ± 0.3	−2.3 ± 0.7	−2.3 ± 0.4	−2.5 ± 0.4[1]	−2.8 ± 0.5[1,2]	−2.7 ± 0.5[1]
LSRe (s^{-1})	2.4 ± 0.3	2.5 ± 0.4	2.5 ± 0.5	2.9 ± 0.6[1]	3.1 ± 0.6[1,2,3]	3.2 ± 0.7[1,2,3]
LSRa (s^{-1})	1.6 ± 0.3	1.9 ± 0.4	1.9 ± 0.3	2.1 ± 0.5[1]	2.2 ± 0.5[1]	1.8 ± 0.7

Within each row, superscripts [1,2,3,4] indicate a value being statistically significantly different from Beagles with no/minimal mitral regurgitation (MR), Cavalier King Charles Spaniels (CKCS) with no/minimal MR, mild MR, and moderate/severe MR, respectively (all Tukey-Kramer-adjusted $P < .05$). All values are reported as mean and standard deviation.

CHF, clinical signs of congestive heart failure; HR, heart rate measured from the ECG during the 3 cycles used for postprocessing of global longitudinal strain (LSt) and strain rates in systole (LSRs), early (LSRe) and late (LSRa) diastole.

Table 4. Global radial strain and strain rates evaluated from the parasternal short axis view.

	Beagle, No/ Minimal MR	CKCS, No/ Minimal MR	CKCS, Mild MR	CKCS, Moderate/ Severe MR	CKCS, CHF	Different Breeds, CHF
n	13	17	14	17	17	14
HR (min^{-1})	99 ± 22	118 ± 24	123 ± 30	135 ± 27[1]	140 ± 12[1]	122 ± 34
RSt (%)	53.1 ± 10.0	55.0 ± 9.8	56.9 ± 6.1	61.9 ± 12.4	62.2 ± 15.7	58.4 ± 17.6
RSRs (s^{-1})	2.9 ± 0.6	3.1 ± 0.7	3.2 ± 0.6	3.5 ± 0.6[1]	3.9 ± 0.6[1,2]	3.6 ± 0.9[1]
RSRe (s^{-1})	−2.4 ± 0.6	−2.9 ± 0.7	−2.8 ± 0.4	−3.3 ± 1.0[1*]	−3.3 ± 0.9[1†]	−3.3 ± 1.1[1‡]
RSRa (s^{-1})	−2.1 ± 0.5	−2.6 ± 0.4	−2.4 ± 0.8	−2.5 ± 0.8[*]	−2.4 ± 0.6[†]	−2.0 ± 0.5[‡]
STI (ms)	35.0 (25.7–43.0)	63.3 (36.7–73.3)	41.8 (33.3–59.3)	40.0 (27.7–60.0)	46.7 (29.5–77.0)	51.5 (24.0–71.0)
SDI (ms)	14.7 (12.2–19.3)	28.7 (17.9–31.3)	18.4 (14.0–26.0)	17.6 (10.8–27.0)	20.0 (12.7–37.5)	21.6 (10.5–30.3)

Within each row, superscripts [1,2,3,4] indicate a value being statistically significantly different from Beagles with no/minimal mitral regurgitation (MR), Cavalier King Charles Spaniels (CKCS) with no/minimal MR, mild MR, and moderate/severe MR, respectively (all Tukey-Kramer-adjusted $P < .05$). All values are reported as mean and standard deviation except for STE and SDI, presented as median and interquartile ranges due to lack of normal distribution.

CHF, clinical signs of congestive heart failure; HR, heart rate measured from the ECG during the 3 cycles used for postprocessing of global radial strain (RSt) and strain rates in systole (RSRs), early (RSRe) and late (RSRa) diastole; SDI, standard deviation of the regional timing of peak radial strain; STI, difference in timing of the peak radial St from the earliest to the latest segment.

Due to fusion of SRe and SRa waves, a total of 4 observations were excluded, resulting in *$n = 16$, †$n = 15$, and ‡$n = 13$, respectively.

Table 5. Significant associations from multiple second-order polynomial regression analyses between global radial ($n = 92$) and longitudinal ($n = 85$) strain and strain rates and conventional echocardiographic indices of MMVD severity and LV remodeling.

STE-Variable	Predictor		
	ARJ/LAA	LA/Ao	LVIDd$_{inc}$
LSt (%)	$P < .0001$ (0.36) ↑	$P < .0001$; $P < .0001$ (0.26) ∩	$P = .0003$ (0.14) ↑
LSRs (s^{-1})	$P < .0001$ (0.50)^{HR} ↑	$P = .0003$; $P = .004$ (0.46)^{HR} ∩	$P = .002$ (0.42)^{HR} ↑
LSRe (s^{-1})	$P < .0001$ (0.39) ↑	$P = .0002$; $P = .002$ (0.27) ∩	$P < .0001$ (0.34)^{BW} ↑
LSRa (s^{-1})	NS	$P = .002$; $P = .002$ (0.24)^{BW} ∩	NS
RSt (%)	$P = .003$ (0.08) ↑	$P = .0008$; $P = .0008$ (0.10) ∩	NS
RSRs (s^{-1})	$P = .001$ (0.32)^{HR} ↑	NS	NS
RSRe*(s^{-1})	$P = .0005$ (0.12) ↑	$P = .0001$; $P = .0003$ (0.15) ∩	NS
RSRa*(s^{-1})	NS	NS	$P = .003$ (0.18)^{HR} ↓

*$n = 88$ due to exclusion of 4 observations with fusion or early and late diastolic strain rates.

Mitral regurgitation in percentage of the left atrium (ARJ/LAA), left atrial-to-aortic root ratio (LA/Ao), and percentage increase in left ventricular internal diameter in diastole (LVIDd$_{inc}$) were all entered separately in models. Please see Table 2 for abbreviations of STE-variables. Age, body weight (BW), sex, heart rate (HR), CKCS (yes/no), and presence of pulmonary hypertension (yes/no) were included as covariates. If a significant second-order polynomial association, marked by ∩, was found, 2 P values are reported: the 1st one representing the predictor itself, and the 2nd one representing the squared derivative. If a significant linear association was found, only 1 P value is reported: ↑ denotes a positive association, whereas a negative association is marked by ↓. The parenthesis represents the adj. R^2 for the final model. A superscript indicates a significant covariate for the respective model: $^{HR}P < .0002$; $^{BW}P < .0001$.

but HR had the highest model R^2. The RSRa decreased with increasing LVIDs$_{inc}$ and HR (both $P < .0001$), whereas no global St or SR variable was associated with E/E′.

Discussion

The present study shows that among dogs with no or minimal MR, no global St or SR variable differed between a predisposed breed and a breed less prone to develop MMVD. Dogs with clinical signs of CHF had increased LSt, LSRs, RSRs, LSRe, and RSRe compared with dogs with no or minimal MR. These variables also increased with degree of MR, when ARJ/LAA was used as a continuous variable. However, many dogs were classified as having an ARJ/LAA of 100% and the dogs with clinical signs of CHF encompassed a wide range of decompensation and LV remodeling severities. Therefore, the LA/Ao also was used as an index of disease severity due to the chronic nature of the MR. Interestingly, all of the above-mentioned longitudinal variables plus LSRa exhibited significant curvilinear associations with LA/Ao. Similarly, significant curvilinear associations were found for RSt and RSRe and the predictor LA/Ao.

A recent study employing the STE technique in small breed dogs with asymptomatic MR, but with echocardiographic signs of cardiac compensation, reported increased RSt, RSRs, and RSRe compared to healthy control dogs.[19] In agreement with this previous study, we detected a significant increase in RSRs and RSRe in dogs with asymptomatic moderate or severe MR compared with dogs with no or minimal MR, whereas the increase in RSt was not reproduced. The findings of significantly increased RSRs and RSRe even in dogs with clinical signs of CHF thus

extend the findings by Smith et al[19] to symptomatic stages of MMVD. Global longitudinal St and SR values were similarly increased in dogs with both asymptomatic and symptomatic moderate or severe MR compared with dogs with no or minimal MR in the present study. To the best of our knowledge, global longitudinal St and SR evaluated by use of STE have not previously been reported in dogs with MMVD. However, a previous study using tissue Doppler imaging in small breed dogs reported increased longitudinal St and SR up to moderate MMVD and decreased variables at severe disease stages.[20] In the present study, LSt, LSRs, and LSRe increased with percentage ARJ/LAA modeled as a continuous variable, whereas curvilinear relationships were found for these variables and LA/Ao. Such curvilinear relationships also were found for RSt and RSRe. These findings indicate increased magnitude and rate of myocardial deformation up to an average LA/Ao ratio of 2.1 followed by an apparent decrease to levels corresponding to dogs with no or minimal or mild MR. The findings in the present study thus support the results previously reported by Wess et al[20] indicating presence of a dynamic change in LV function throughout the course of MMVD. Longitudinal St and SR represent the magnitude and rate of shortening or lengthening of the LV, whereas radial St and SR represent wall thickening or thinning during the cardiac cycle. These factors, contributing to the emptying and filling of the left ventricle, thus can be assessed as being descriptive of LV function. Based on the significant polynomial associations, our findings suggest that small-to-medium-sized dogs with MMVD exhibit augmented LV function up to moderate disease stages. At severe symptomatic MMVD stages, defined by severe left atrial enlargement, LV function appears to decrease to
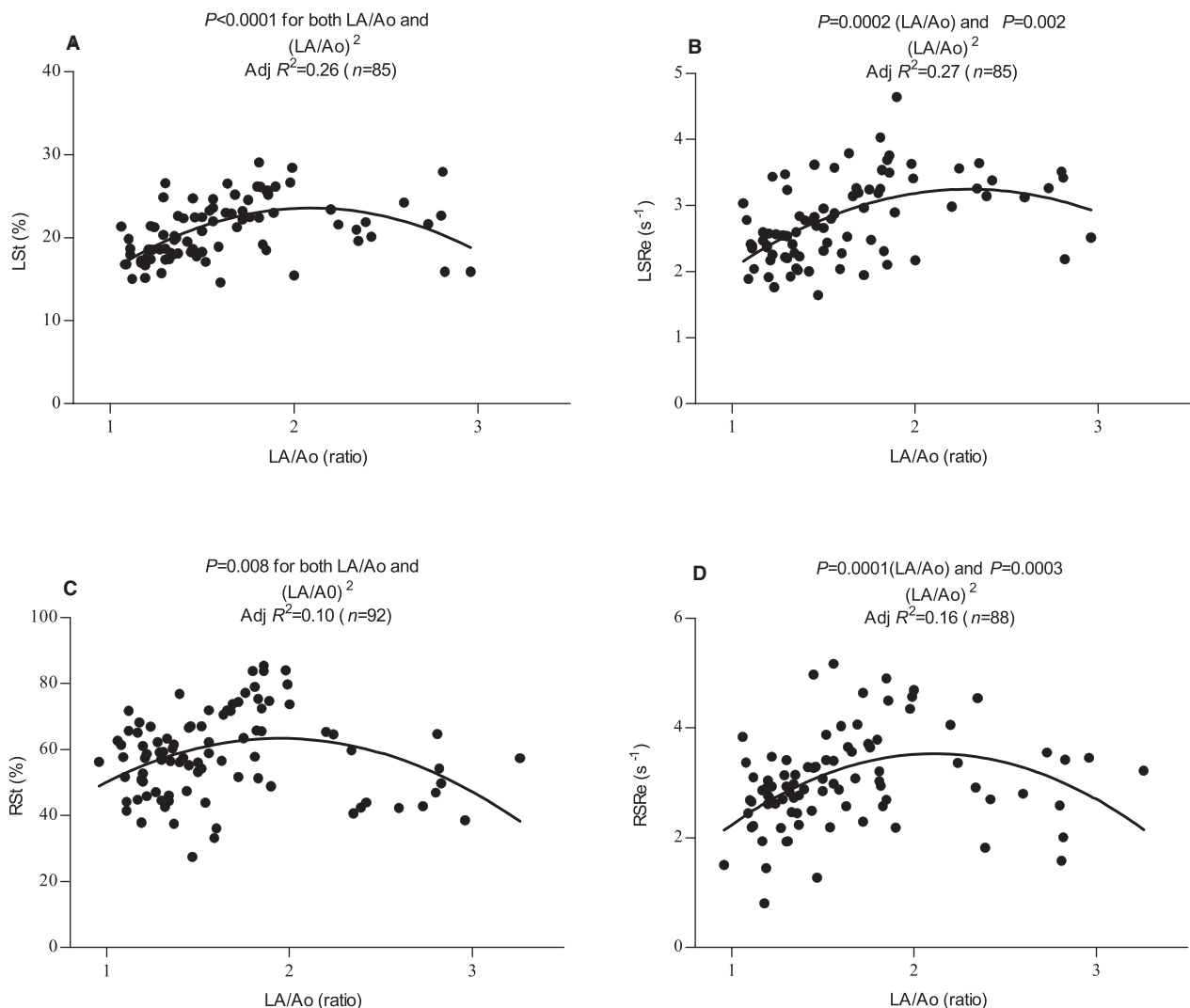
Fig 2. Line of fit from the multiple polynomial regressions of global longitudinal systolic strain (LSt) (A), global longitudinal early diastolic strain rate (LSRe) (B), global radial systolic strain (RSt) (C), and global radial early diastolic strain rate (RSRe) (D) on left atrial-to-aortic root ratio (LA/Ao) and $(LA/Ao)^2$. Please note that numerical values were used for statistical analysis. Variable estimates: LSt = $-6.37 \times (LA/Ao)^2 + 26.68 \times LA/Ao - 4.33$. Vertex: 2.1; RSt = $-14.68 \times (LA/Ao)^2 + 57.30 \times LA/Ao - 14.68$. Vertex: 2.0; LSRe = $-0.73 \times (LA/Ao)^2 + 3.36 \times LA/Ao - 0.51$. Vertex: 2.3; RSRe = $-1.02 \times (LA/Ao)^2 + 4.27 \times LA/Ao - 1.15$. Vertex: 2.1.

a level comparable to dogs with no or minimal and mild MR. However, such a dynamic change was partially obscured in group-wise analyses. Dogs with CHF showed a large spread in STE-derived variables, and therefore a significant decrease in St and SR variables compared with dogs with compensated MR was not found.

Although deformation indices, in particular SRs, have been reported to reflect LV function at least partially independently of hemodynamic load,[21,22] we cannot rule out that our findings reflect changes in loading conditions, LV volume, and sympathetic tone associated with the presence of MR. Under experimental conditions, augmented St and SR were reported with increased LV volume and HR, whereas increased afterload decreased St and SR.[21,22] The increased preload and decreased afterload associated with the

presence of MR might therefore increase St and SR values. In the present study, a notable effect of sympathetic tone on SRs variables was supported by the finding of HR being a significant covariate in all models predicting SRs, and the fact that HR had the highest model R^2 for the respective models. On the other hand, the influence of increased preload might be less pronounced because no St or SR variable was associated with E/E′, a variable suggested to reflect LV filling pressure.[23] This finding is in agreement with a study using STE in healthy dogs.[9]

Despite a large spread, the LVIDs$_{inc}$ was increased approximately 30% above the expected values in most dogs with clinical signs of CHF. Up to 20% increase in LVIDs from normal reference range has previously been used as an indicator of mild LV systolic dysfunction.[24] Some degree of systolic dysfunction among the

included dogs with clinical signs of CHF was thereby indicated by conventional echocardiographic indices. Hence, advantages in using STE for the evaluation of LV function were not convincingly demonstrated by the present study; findings which are concordant with the result of Smith et al.[19]

Significantly decreased LV function before the onset of clinical signs of CHF was not detected in the present study. Our findings thus support previous studies suggesting that clinical signs in small breed dogs with MR are not caused mainly by LV dysfunction, but are associated with the severity of the MR itself, leading eventually to increased pulmonary pressure.[24,25]

No St or SR variable differed significantly between Beagles and CKCS with no or minimal MR or between CKCS and other breeds with clinical signs of CHF whereby presence of breed differences among small-to-medium-sized dogs was not indicated by the present study.

The present study shows that the STE technique is feasible in dogs with MMVD, especially in the SAX view. Obtaining a satisfactory tracking of all segments in the 4-Ch view was challenging, however. Spherical and fast-beating hearts were more difficult to track and inevitably resulted in comparable lower FR per cardiac cycle. However, HR was only a significant covariate in models predicting SRs. Future studies might benefit from the acquisition of single wall images instead of inclusion of the entire left ventricle when evaluating STE-derived St and SR in dogs with enlarged hearts, increased HR or both.

Statistically significant intersegmental differences in STE-derived longitudinal St and SR were not found in a previous study in healthy dogs.[10] Therefore, using an average of segments seems to be an acceptable representation of the entire LV deformation. On the other hand, the calculation of global values based on < 6 approved segments can reasonably be questioned. However, the repeatability of global St and SR values calculated from images with $\geq$ 4 approved segments was acceptable for all variables except RSRa, thus validating this approach for the calculation of global St and SR. Nonetheless, segmental differences within individual dogs might be obscured by the calculation of global values. Despite marked variation, a previous study on dogs with MMVD did not find statistically significant differences in degree of fibrosis and arteriolar narrowing by comparison of different localizations within the LV wall, except for the papillary muscles.[2] Thus, segmental differences in myocardial deformation in dogs with MMVD might not be anticipated either.

An important limitation is the very high CV of RSRa, STI, and SDI found in the present study, and these findings presumably limit the clinical utility of these variables in dogs with MMVD. The reason for the high CV of STI and SDI indices might be a reflection of an excessively low frame rate-to-heart rate ratio. The FR was in all instances 2/3 of the HR, but this FR might still be too low to permit accurate timing and thus evaluation of synchronicity.

Another important limitation is the medication administered to dogs with advanced MMVD, which included drugs known to affect cardiomyocyte contractility and cardiovascular load.[26,27] Moreover, dogs with clinical signs of CHF were significantly older, and Beagles with no or minimal MR significantly heavier than all other dog groups. Longitudinal St and SR have been shown to decrease with increasing age in humans,[28] but age was not a statistically significant covariate in any final models in the present study. On the other hand, although no statistically significant differences were found between Beagles and CKCS with no or minimal MR, BW was a significant covariate in 2 models predicting longitudinal SRe and SRa.

Several associations, especially with radial St and SR variables, showed a low adjusted R^2. Because no radially oriented fibers exist in the heart, the wall thickening, ie, the radial deformation, is the result of both longitudinal and circumferential shortening as well as of the shear between the oppositely oriented muscle fibers in the subendocardial and subepicardial layers. Longitudinal and circumferential deformations have been shown to change at different time points during experimental canine LV dysfunction[29] and it has been suggested that they might even compensate each other.[30] Therefore, these forces might affect the radial deformation individually, and maybe even oppositely directed, during compensatory stages of volume overload. This could explain why radial deformation indices reflected only a minor part of the variation among dogs in the present study. Generally, radial deformation variables had less repeatability than the corresponding longitudinal variables, an observation that might also have been of importance for the findings of fewer statistically significant associations and lower adjusted R^2 values with radial variables.

No association between STE variables and presence of PHT was observed in the present study. However, presence of PHT was diagnosed by use of Doppler echocardiography and the prevalence of PHT thus potentially might be underestimated, and potential associations be obscured in the present study. Finally, evaluation of the size of the regurgitant jet by use of color Doppler is not accurate because it allows only for semi-quantification and is affected by factors such as systemic and pulmonary blood pressure levels and the spatial orientation of the regurgitant jet. Moreover, the ARJ/LAA was subjectively estimated by eye in increments of 5%. Nonetheless, the significant associations found with percentage ARJ/LAA were supported by findings using other echocardiographic indicators of MMVD severity, and such potential inaccuracy in the estimation of the size of the regurgitant jet is not suspected to have influenced the conclusions drawn from the present study.

The present study showed an apparent increase in global longitudinal and radial St and SR in both systole and early diastole in dogs with increasing severity of MMVD, as assessed by increasing degree of MR on multiple regression analyses. However, all of the above variables, except global radial systolic

SR, exhibited curvilinear relationships with LA/Ao, indicating presence of an augmented LV function up to an average LA/Ao ratio of 2.1 followed by an apparent decrease in LV function with more pronounced enlargement of the left atrium, but this decrease was to a level similar to that observed in clinically healthy dogs. The clinical relevance of these findings, including an evaluation of the timing of the decrease in these deformation variables and their relation to survival time and medication, should be investigated further.

Footnotes

Acknowledgments

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