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# Decreased Systolic Function and Inadequate Hypertrophy in Large and Small Breed Dogs with Chronic Mitral Valve Insufficiency

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**Background:** Systolic dysfunction associated with chronic mitral valve insufficiency (CMVI) has been demonstrated in experimental animal models and large breed (LB) dogs but has been reported as an uncommon finding in small breed (SB) dogs with naturally occurring disease. It has been suggested the myocardial failure could be, in part, because of an insufficient increase in left ventricular mass.

**Hypothesis:** To test if SB and LB dogs with CMVI and moderate heart failure have systolic dysfunction and if they have adequate eccentric hypertrophy.

**Animals:** Data from 38 SB and 18 LB dogs affected with CMVI were compared retrospectively with results from 2 groups of normal dogs (17 SB and 32 LB)

**Methods:** Systolic function was investigated echocardiographically by using percentage fractional shortening (FS), the ratio between observed and expected end-systolic diameter (ESD/ESDe), and end-systolic volume index (ESVI). Left ventricular hypertrophy was estimated by using the ratio between the thickness of the left ventricular free wall and the radius in diastole (h/R).

**Results:** Both affected SB and LB dogs had a significantly increased FS and ESVI (FS% SB 45.6 + 8.04 versus 40.06 + 8.9, $P < .05$; FS% LB 33.64 + 8.61 versus 27.3 + 7.3 $P < .05$; ESVI SB 30.0 ± 2.3 mL/m$^2$ versus 21.18 ± 13.9 mL/m$^2$, $P < .05$; ESVI LB 83.22 ± 43.84 mL/m$^2$ versus 36.43 ± 13.30 mL/m$^2$ versus $P < .001$). The h/R in affected animals was decreased (0.53 ± 0.11 versus 0.41± 0.12, $P < .05$ SB; 0.47 ± 0.11 versus 0.38 ± 0.09, $P < .05$, LB).

**Conclusions and Clinical Importance:** Data from this study indicate that dogs with moderate heart failure caused by CMVI have systolic dysfunction. Inadequate hypertrophy of the left ventricle may be, in part, responsible for this finding.

**Key words:** Dogs; Heart; Heart failure; Mitral regurgitation; Myxomatous mitral valve disease; Volume overload.

Chronic mitral valve insufficiency (CMVI), caused by myxomatous degeneration of the valve, is the most common acquired heart disease in dogs. Systolic dysfunction has been reported as an uncommon finding in affected small breed (SB) dogs, and, if present, it has been considered an end-stage finding in CMVI or the effect of complicating factors, such as multiple small intramural myocardial infarcts.[1–3] Studies of experimentally induced chronic mitral regurgitation in dogs suggest that an inadequate degree of ventricular hypertrophy develops in this condition and could be one mechanism that contributes to the left ventricular dysfunction observed both in people and in experimental dogs.[4,5] Wall stress imposed by pure volume overload has been hypothesized to be an insufficient stimulus for myocardial hypertrophy and in a large breed (LB) canine experimental model of CMVI this condition was associated with inadequate left ventricular hypertrophy, culminating in systolic dysfunction.[5] Patients with CMVI have reduced afterload, because blood is regurgitated in the left atrium, which is a relatively low-pressure chamber. Because increased afterload is one of the stimuli for hypertrophy represented by increased afterload, pure volume overload is an insufficient stimulus for hypertrophy.

Echocardiography is a useful tool for noninvasive evaluation of systolic function.[6,7] However, most of the indices commonly used to evaluate systolic function, such as fractional shortening (FS), ejection fraction (EF), end-systolic volume index (ESVI), are strictly dependent on intrinsic contractility, preload, afterload, and wall stress. Therefore, any variation in these indices must take into account these factors. Other variables that can influence the echocardiographic evaluation of systolic function include age; sex; weight; breed; comorbid factors, eg, hypothyroidism; and hydration status. In dogs, weight and breed especially appear to be important variables influencing echocardiographic measurements.[8–11] FS and EF estimated by M-mode measurements decrease with increasing body weight (BW) and generally in LB dogs.[8,12] ESVI has been proposed as a more accurate parameter of systolic dysfunction, because it is mainly dependent on afterload and contractility, and is relatively independent of preload.[13] Values >30 mL/m$^2$ are considered to indicate systolic dysfunction.[3,13] However, although ESVI represents a volume index, it is calculated by using the Teicholz formula[14] from an M-mode linear measurement, which means that it may also be influenced by BW and breed. Furthermore, any error in M-mode linear measurement is raised to the power of 3 according to the formula used to calculate ESVI.

In a previous study, we demonstrated that LB dogs affected with mitral valve insufficiency more commonly have moderate-to-severe systolic dysfunction compared with SB dogs.[15,16] This difference could be because of decreased contractility in LB dogs compared with SB

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dogs, or because LB dogs have different normal systolic values, which means that systolic function could be over- or underestimated in both groups. To test this hypothesis, we compared systolic function by using echocardiography in LB and SB dogs affected with CMVI with those of 2 groups of normal dogs. Moreover, to test if systolic dysfunction could be a consequence of inadequate hypertrophy, we also evaluated the degree of left ventricle eccentric hypertrophy in LB and SB dogs with CMVI.

## Material and Methods

### *Study Design*

The medical records of dogs examined at the Small Animal Hospital of the Faculty of Veterinary Medicine of Torino between January 2000 and October 2004 were reviewed. From these records, 38 consecutive dogs weighing >20 kg (LB group) and 18 consecutive dogs weighing <15 kg (SB group) affected by mitral valve disease were selected. All dogs were presented for cardiology consultation because of previous identification of a heart murmur or because of the presence of clinical signs indicating a cardiovascular disorder (eg, cough, exercise intolerance). Forty-nine normal dogs were examined prospectively during the period from September 2003 to October 2004. The dogs were divided into 2 groups according to their BW: normal SB dogs (NSB) who weighed <15 kg (n = 17) and normal LB dogs (NLB) who weighed >20 kg (n = 32). All dogs had been presented for annual physical examinations. Dogs were considered normal based on the absence of clinical signs of heart disease, normal systolic blood pressure (SBP), and the absence of echocardiographic abnormalities. The 8 Doberman Pinchers and the 3 Great Danes included in LB group were part of a screening program for dilated cardiomyopathy and did not have any echocardiographic evidence of increased left ventricular dimensions or arrhythmias on 2-minute ECG recordings, in the past 2 years on at least 2 screening echocardiographic examinations.

***Inclusion Criteria***. Affected dogs were those with recognition of mitral valve prolapse (MVP); any degree of mitral valve leaflet thickening by 2-dimensional (2-D) echocardiography or the identification of any degree of mitral valve regurgitation, with or without mitral valve lesions by color-Doppler examination. To be included in the analysis, dogs must have had at least one of these abnormalities. Left ventricular FS had to be >20%, and left ventricular ejection fraction (EF) had to be >40%. Left atrium aortic root ratio (LA/Ao), evaluated by using the B-mode method, had to be >1.7. Dogs must have been presented with signs of heart failure (eg, exercise intolerance, dyspnea, cough) and have had documented past evidence of pulmonary edema on thoracic radiographs for at least 3 months. Thus, each included dog was classified as class II heart failure according to International Small Animal Health Cardiac Council (ISACHC) recommendations.[17] All affected dogs were on therapy with benazepril (0.5 mg/kg PO q24h) or enalapril (0.5 mg/kg PO q12h) and furosemide (mean dosage 1.85 mg/kg PO q12h; range, 0.8–2.5 mg/kg PO q12h) at least for 3 months.

***Exclusion Criteria***. Exclusion criteria included the presence of systemic hypertension, congenital heart diseases, or acquired cardiovascular disorders that primarily or secondarily affect the mitral valve (eg, bacterial endocarditis, dilated cardiomyopathy). Blood pressure was measured noninvasively by Doppler sphygmomanometry,[a] and hypertension was defined as systolic arterial blood pressure (SBP) >180 mm Hg.[18] Mitral endocarditis was excluded based on clinical findings, CBC, and serum biochemistry, and the lack of large vegetative lesions, with a heterogeneous appearance on echocardiography.[19] Dilated cardiomyopathy was excluded based on the presence of valve changes consistent with myxomatous mitral valve disease and MVP and the absence of echocardiographic criteria such as FS < 20%, and left ventricular EF <40%.

***Echocardiography***. All dogs underwent complete echocardiographic examination, which included transthoracic 2-D, M-mode, spectral and color flow Doppler studies. Transducer arrays of 2.5–3.5 MHz (LB and NLB group) and 3.5–5.0 MHz (SB and NSB group) were used.[b] Examinations were performed in conscious, unsedated dogs. Right parasternal M-mode recordings were obtained from short-axis views with the dogs positioned in right lateral recumbency, and the 2-D echocardiograms were obtained in accordance with techniques described elsewhere.[20,21]

The presence of MVP and mitral valve thickening was evaluated from the right parasternal long-axis view, the right parasternal 4-chamber view,[22,23] and left apical 4-chamber view.[24] MVP was defined as any systolic displacement of one or both mitral valve leaflets basal to the mitral annulus, observed at least in two of these views.[15]

Mitral valve regurgitation was evaluated by using color Doppler from the right parasternal long-axis view and left apical view, and its severity was subjectively assessed by using the left apical 4-chamber view as described below.

### *Echocardiographic Measurements*

All echocardiographic measurements were made by 2 investigators (MB, AT) and were reviewed by 1 investigator (MB) who examined the videotape recordings. A mean of 3 consecutive measurements in dogs with sinus rhythm, and 5 consecutive measurements in dogs with atrial fibrillation (AF) was used for each measurement. M-mode measurements were obtained according to the leading-edge-to-leading-edge method.[25] These included left ventricular free-wall thickness in diastole (h), left ventricular end-diastolic diameter (EDD) and end-systolic diameter (ESD). Left ventricular radius (R) was obtained by dividing EDD by 2. FS was calculated by using the following formula: [(EDD − ESD)/EDD) × 100]. Based on BW, the expected values for EDD and ESD were calculated, according to Cornell et al[11] by using the formulas: $EDDe = 1.53 \times BW^{0.294}$ and $ESDe = 0.95 \times BW^{0.315}$. The ratio between observed and expected values of EDD and EDS were calculated (EDD/EDDe; ESD/ESDe) to allow comparisons between groups of dogs with different body size. The end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated by using the Teicholz method: $EDV = [7 \times (EDD)^3] / (2.4 + EDD)$ and $ESV = [7 \times (ESD)^3]/(2.4 + ESD)$,[14] and values were successively indexed for body surface area to obtain the end-diastolic volume index (EDVI) and the ESVI. The h/R ratio was used as a parameter of left ventricular hypertrophy.[26] Data were compared in dogs of similar size.

### *Statistical Analysis*

Statistical analysis was performed by using a commercial statistical package (Instat 306).[c] Normally distributed data were identified by using the Shapiro Wilk normality test. Within the 2 groups of normal dogs, the mean difference for observed EDD and ESD and expected values was examined by using a paired Student's *t*-test. Among the 4 groups of dogs, the mean differences for each of the studied variables were examined by using a unpaired Student's *t*-test. The chi-square test was used to compare proportions between sexes. Equality of variances was assessed by the *F*-test. Differences were considered significant if $P < .05$. Data are reported as mean ± standard deviation.

**Table 1.** M-mode echocardiographic parameters of left ventricular function in normal small and large breed dogs.*

| | SB Group (n = 17) | LB Group (n = 32) | *P* Value |
|---|---|---|---|
| Dog weight (kg) | 7.3 ± 3.1 | 36.9 ± 13.00 | <.001 |
| SBP (mm Hg) | 159.25 ± 12.8 | 141.0 ± 17.4 | <.05 |
| EDD (cm) | 2.60 ± 0.47 | 4.37 ± 0.50 | <.001 |
| EDDe (cm) | 2.63 ± 0.32 | 4.67 ± 0.29 | <.001 |
| ESD (cm) | 1.52 ± 0.48 | 3.04 ± 0.46 | <.001 |
| ESDe (cm) | 1.70 ± 0.22 | 2.69 ± 0.15 | <.001 |
| EDD/EDDe | 0.99 ± 0.13 | 0.94 ± 0.10 | <.001 |
| ESD/ESDe | 0.89 ± 0.21 | 1.13 ± 0.15 | <.001 |
| FS (%) | 40.06 ± 8.9 | 27 ± 7.3 | <.001 |
| EF (%) | 70.75 ± 9.20 | 56.85 ± 10.2 | <.05 |
| ESVI (mL/m$^2$) | 21.18 ± 13.90 | 36.43 ± 13.30 | <.001 |
| EDVI (mL/m$^2$) | 70.5 ± 26.5 | 84.10 ± 20.21 | NS |
| LA/Ao | 1.22 ± 0.31 | 1.27 ± 0.20 | NS |
| h/R | 0.53 ± 0.11 | 0.47 ± 0.11 | NS |

SB, small breed; LB, large breed; SBP, systolic blood pressure; EDD, end diastolic diameter; ESD, end-systolic diameter; EDDe, expected end diastolic diameter; ESDe, expected end-systolic diameter; FS, fractional shortening; EF, ejection fraction; ESVI, end-systolic volume index; EDVI, end diastolic volume index; LA/Ao, left atrium aortic root ratio; h/R, left ventricular free-wall thickness/left ventricle diastolic radius ratio; NS, not significant.

* Data are expressed as mean values ± standard deviation.

## Results

### *Normal Dogs*

The NSB group included 17 dogs (5 males, 12 females): 5 mongrels; 4 Yorkshire Terriers; 2 Shi-Tzu; 2 English Cocker Spaniels; 1 each Dachshund, Jack Russell Terrier, French Bulldog, and Pomeranian. The mean age was 8.7 ± 3.5 years (range, 1–14 years), and the mean weight was 7.3 ± 3.1 kg (range, 3.5–13 kg). The NLB group included 32 dogs (17 males, 15 females): 8 Dobermann Pinchers; 6 German Shepherds; 5 mongrels; 3 Boxers; 3 Great Danes; 2 Rottweilers; 1 each Bulldog, Alaskan Malamute, Labrador Retriever, Collie, and Golden Retriever;. The mean age was 5.3 + 3.7 years (range, 1–9 years), mean weight was 36.9 + 13.00 kg (range, 21–67 kg). Normal SB dogs were significantly older ($P < .05$). There were no significant differences by sex between the 2 groups ($P = .19$). SBP was significantly higher in NSB (Table 1). All dogs were judged to have a normal body condition scores. The M-mode derived variables of left ventricular function in the 2 groups are summarized in Table 1. Normal SB dogs had higher FS and EF, and lower ESVI compared with NLB dogs. No significant difference in EDVI was found between the 2 groups. The observed EDD (2.60 ± 0.47 cm) and ESD (1.52 ± 0.48 cm) were not significantly different compared with expected values (EDDe = 2.63 ± 0.32 cm, $P = .73$; ESDe = 1.7 ± 0.22 cm, $P = .07$) in NSB; whereas, observed EDD (2.60 ± 0.47 cm) was significantly smaller and ESD was significantly larger (3.04 ± 0.46 cm) compared with expected values (EDDe = 4.67 ± 0.29 cm, $P < .001$; ESDe = 2.69 ± 0.15 cm, $P < .001$) in NLB. However, in NLB, both EDD and ESD values were within 95% confidence intervals of the expected values. The h/R ratio was similar in both groups.

### *Results of Normal Dogs Versus Dogs with CMVI*

The SB dogs with CMVI included 6 mongrels, 4 Yorkshire Terriers, 3 Dachshunds, 3 Miniature Poodles, 1 Epanieul Breton, and 1 Miniature Pincher. The group consisted of 16 males and 2 females. The mean weight was 11 ± 2.7 kg (range, 3–15 kg), and the mean age was 11 ± 3.2 years (range, 9–14 years). The LB dogs with CMVI (29 males, 9 females) included 28 German Shepherds, 5 Maremmano Shepherds, 2 mongrels, 1 Saluki, 1 Doberman Pincher, and 1 Dalmatian. The mean weight was 34.7 ± 7.4 kg (range, 21–40 kg) and the mean age was 9.5 ± 3.4 years (range, 8–15 years). Both SB and LB dogs with CMVI were significantly older compared with the normal dogs ($P < .05$) and had a significantly lower SBP ($P < .05$). All affected dogs had normal body condition scores. FS, EDD/EDDe, ESD/ESDe, ESVI, and EDVI were significantly higher in affected SB and LB dogs compared with normal dogs of similar size (Tables 2 and 3). The h/R in affected animals was decreased compared with normal groups ($P < .05$).

## Discussion

The effect of pure volume overload secondary to CMVI on left ventricular function is controversial. Although many studies have identified normal left ventricular function, others found a reduction.[4,13,27–29] The discrepancies observed among these studies may be related to the duration of volume overload, amount of hypertrophy produced, or the type of experimental volume overload examined. Data from our study suggest that both SB and LB affected with CMVI and moderate HF have some degree of systolic dysfunction. Myocardial failure (MF) has been reported as an uncommon finding in SB dogs affected by CMVI,

**Table 2.** Echocardiographic parameters of left ventricular function in small breed normal dogs and dogs affected with mitral valve disease. Data are expressed as mean values ± standard deviation.

| | Normal SB (n = 17) | Affected SB (n = 18) | *P* Value |
|---|---|---|---|
| Dog weight (kg) | 7.3 ± 3.1 | 11 ± 2.7 | NS |
| Age (years) | 8.7 ± 3.5 | 11 ± 3.2 | <.05 |
| FS (%) | 40.06 ± 8.9 | 45.6 ± 8.04 | <.05 |
| EDD/EDDe | 0.99 ± 0.13 | 1.28 ± 0.14 | <.001 |
| ESD/ESDe | 0.89 ± 0.21 | 1.11 ± 0.13 | <.001 |
| ESVI (mL/m$^2$) | 21.18 ± 13.90 | 30.0 ± 2.30 | <.05 |
| EDVI (mL/m$^2$) | 70.5 ± 26.5 | 138.8 ± 47.8 | <.05 |
| LA/Ao | 1.22 ± 0.31 | 2.24 ± 0.31 | <.001 |
| h (cm) | 0.71 ± 0.04 | 0.74 ± 0.18 | NS |
| R (cm) | 1.14 ± 0.24 | 1.85 ± 0.41 | <.001 |
| h/R | 0.53 ± 0.11 | 0.41 ± 0.12 | <.05 |

SB, small breed; NS, not significant; SBP, systolic blood pressure; FS, fractional shortening; EDD, end diastolic diameter; ESD, end systolic diameter; EDDe, expected end diastolic diameter; ESDe, expected end systolic diameter; ESVI, end-systolic volume index; EDVI, end diastolic volume index; LA/Ao, left atrium aortic root ratio; h/R, left ventricular free wall thickness/left ventricle diastolic radius ratio.

whereas it has been reported to be more common in LB dogs[2,15,16,30] and humans.[31–33] In a previous study, we compared systolic function in SB and LB dogs with mitral valve disease showing that LB had decreased systolic function compared with SB when using previously reported reference ranges.[15,16] Body weight and size are 2 of the factors that could influence some of the echocardiographic measurements most commonly used for evaluation of systolic function such FS and ESVI.[8,11] Therefore, our previous results could have been influenced by the different size of the 2 groups of dogs studied. The current study shows that NSB had significantly higher FS, EF, and lower ESVI compared with NLB dogs, whereas EDVI was not different between the 2 groups. To compensate for differences in BW, we calculated expected EDD and ESD, as described by Cornell et al[11] and found no differences among NSB. In LB dogs, although mean observed values were different from the mean expected, they were within the 95% reference interval for expected values for that particular BW. ESVI was lower in SB dogs and higher in LB to what it is commonly reported in the normal reference values,[3,34] and this finding is further supported by the finding that the observed values were similar to those expected in normal dogs. These differences could be because of a different contractility pattern. Indices of systolic function, such as the FS, EF, and ESVI, are obtained often by using M-mode short-axis measurements of the LV, but they assume a uniform systolic contraction in all planes, which may not be true. Therefore, B-mode estimation of the EF, such as the area-length method, could more accurately measure global systolic function, measuring contractility both on the short and long axis. Indeed, we observed that EF calculated by the area-length method did not differ between the 2 groups of normal SB and LB dogs, suggesting that LB dogs have systolic function more prominently directed on the long axis.[d] The observation that EDVI was similar in the 2 groups and that SBP was significantly lower in the LB group, further supports our hypothesis of a different pattern of ventricular contraction. In fact, this situation would lead to a smaller ESV. Eccentric hypertrophy leading to an increase in short-axis diameter would increase meridional stress, and patients with a contractility pattern directed mainly along the long axis, as may occur in LB dogs, may

**Table 3.** Echocardiographic parameters of left ventricular function in large breed normal dogs and dogs affected with mitral valve disease. Data are expressed as mean values ± standard deviation.

| | Normal LB (n = 32) | Affected LB (n = 38) | *P* Value |
|---|---|---|---|
| Dog weight (kg) | 36.9 ± 13.00 | 34.71 ± 7.42 | NS |
| Age (years) | 5.3 ± 3.7 | 9.5 ± 3.4 | <.001 |
| FS (%) | 27.3 ± 7.3 | 33.64 ± 8.61 | <.05 |
| EDD/EDDe | 0.94 ± 0.10 | 1.30 ± 0.17 | <.001 |
| ESD/ESDe | 1.13 ± 0.15 | 1.30 ± 0.27 | <.001 |
| ESVI (ml/m$^2$) | 36.43 ± 13.30 | 83.22 ± 43.84 | <.001 |
| EDVI (ml/m$^2$) | 84.10 ± 20.21 | 133.80 ± 50.75 | <.05 |
| LA/Ao | 1.27 ± 0.20 | 2.20 ± 0.31 | <.001 |
| h (cm) | 1.05 ± 0.18 | 1.02 ± 0.17 | NS |
| R (cm) | 2.27 ± 0.38 | 2.72 ± 0.47 | <.05 |
| h/R | 0.47 ± 0.11 | 0.38 ± 0.09 | <.05 |

LB, small breed; NS, not significant; SBP, systolic blood pressure; FS, fractional shortening; EDD, end diastolic diameter; ESD, end systolic diameter; EDDe, expected end diastolic diameter; ESDe, expected end systolic diameter; ESVI, end-systolic volume index; EDVI, end diastolic volume index; LA/Ao, left atrium aortic root ratio; h/R, left ventricular free-wall thickness/left ventricle diastolic radius ratio.

manifest more evident systolic dysfunction. FS and EF are influenced by different factors such as preload, afterload, contractility and heart rate, whereas ESVI is considered to be primarily influenced by contractility, and afterload. Because EDVI is an indicator of preload, we can assume there were no differences in preload among groups. On the other hand, SB dogs have a higher mean SBP value, which should lead to a decrease in FS. To the contrary, FS was higher in this group.

Both groups of affected dogs had significantly increased of FS, ESVI, and EDVI compared with normal control dogs of similar size. Increases in FS and EDVI were not unexpected in patients with volume overload. In fact, increased preload with a preserved or partially preserved contractility will increase FS and increase EDVI because of the development of eccentric hypertrophy. Both groups had a significantly increased mean ESD/ESDe and mean ESVI. In fact, mitral valve insufficiency could be considered as a condition of pure volume overload. In this condition, systolic dysfunction is echocardiographically recognized by increased values of ESVI, and by values of FS near the lower end of the reference range.[13,35] Because both groups had SBP within the normal reference range, higher ESVI compared with normal controls should indicate that both had systolic dysfunction, and this conclusion also is supported by the increased ESD/ESDe ratio in both groups of diseased dogs. In fact, ESVI is estimated by the ESV indexed to body surface area, and both of these 2 parameters are influenced by BW. Recently, it was demonstrated that many M-mode–derived measurements can be more accurately predicted by using a function involving the cubic root of the BW.[11] Thus, our expected values correct for possible differences associated with differences in BW. Some normal SB dogs have ESVI of 30 mL/m$^2$ or slightly more, and systolic dysfunction should not be based only on an evaluation of this parameter. The indication of MF in SB dogs with CMVI and moderate HF is noteworthy. Clinical signs of congestive HF in SB may be mainly caused by the severity of valvular regurgitation, and clinical signs of disease may be primarily from increased pulmonary venous pressure and pulmonary edema and less from reduced forward cardiac output.[36] Recognition of systolic dysfunction in earlier stages of HF suggests that systolic dysfunction may contribute to the progression of clinical signs of disease, as has been reported in humans and dogs.[1,12,15,29] However, dogs with acute chordal rupture present with acute onset of signs because of severe pulmonary edema and maintain a relatively preserved systolic function. Also, all dogs in this study had chronic moderate HF and to be included they had to have signs for at least 3 months and not signs of acute pulmonary edema during this time. Several hypotheses could explain the development of MF in dogs with mitral valve insufficiency. In experimentally induced chronic mitral regurgitation in dogs, the decreased number of myofibrils in cardiomyocytes and decreased fractional rate of protein turnover seem to contribute to MF, leading to an insufficient increase in LV mass.[3,4,36] The inadequate hypertrophy that develops with CMVI could be one mechanism that contributes to the left ventricular dysfunction observed both in people and in experimental dogs.[37] In this study, we evaluated the degree of eccentric hypertrophy by using the h/R ratio. In pressure overload, systolic stress may trigger the production of new sarcomeres assembled in parallel, thereby increasing wall thickness, whereas in the volume overload of valvular regurgitation, an increase in diastolic stress causes replication of sarcomeres in series, thereby increasing myocyte length. This condition leads to eccentric hypertrophy with a normal h/R ratio.[26] Eventually, this effect normalizes systolic but not diastolic wall stress. Wall stress imposed by pure volume overload may not be a very potent stimulus for cardiac hypertrophy, and, in a canine experimental model of CMVI, this condition was associated with inadequate left ventricular hypertrophy, culminating in systolic dysfunction.[4] We observed that, in both LB and SB dogs, posterior wall thickness was not different from normal dogs, whereas LV radius was increased so that the h/R ratio was decreased compared with normal dogs. These data indicate that end-diastolic wall stress is increased in dogs with pure volume overload and chronic moderate HF, and agree with results of experimental studies in dogs.[38,39] With left ventricular enlargement, meridional wall stress increases more than does circumferential wall stress.[26,40] Because LB dogs could have a contractility pattern more oriented on the long axis, increased meridional stress could be responsible for the more severe systolic dysfunction observed in LB dogs with CMVI.

### *Study Limitation*

One limitation of this study was the inability to exclude with certainty concurrent diseases of either a systemic or a cardiac nature that could have affected systolic dysfunction. Although we used recommended criteria for the diagnosis of the disease,[1,2,23] other undefined systemic or metabolic conditions (eg, malignancies) could have affected myocardial function. Recently, the presence of intramural arteriosclerosis and fibrosis in the myocardium of dogs with CMVI has been described, but the role of these findings in the pathogenesis of the disease is unclear.[e] Although LB dogs included in the study were presented with mitral valve lesions typical of MVP and degenerative valvular disease, some of the dogs could have another concomitant primary myocardial disease, such as dilated cardiomyopathy (DCM). However, one of the inclusion criteria to be fulfilled was a FS $>$ 20%, and it is unlikely that dogs with a FS $>$ 20% and with moderate HF would have DCM. This conclusion would support MF as being secondary to primary mitral valve dysfunction rather than a primary event.[41]

ESVI represents a global index of ventricular function and does not represent contractility at a cellular level. Therefore, contractility dysfunction at the cellular level could occur before it can be detected by using an echocardiographic index such as ESVI.

Another possible limitation of the study is that systolic function can be affected by age.[6] Affected dogs of this study were significantly older than the normal

dogs. However, to the knowledge of the authors, no published study has evaluated systolic function in normal young and aged dogs.

One of the possible factors influencing left ventricular hypertrophy and systolic dysfunction in pure volume overload is the duration of the disease. Affected dogs of our study were retrospectively selected, and they had signs of HF that had been present a variable period of time, which may have influenced our results. However, all dogs with CMVI were classified with class II ISACHC HF, and all of them had clinical signs of HF for at least 3 months. Moreover, none of them had a history of acute decompensation within the last month. Chronic disease also is suggested by the increased LA/Ao root ratio of the diseased dogs. Finally, an experimental study showed that dogs with induced CMVI did not develop left ventricular hypertrophy in response to decreased contractile function, and it is unlikely that this factor influenced our data.[36]

Finally, it is possible that ongoing therapy, which may affect loading conditions, could have influenced the results. All affected dogs in this study were treated with an angiotensen converting enzyme inhibitor and furosemide at standard dosages, at least for 3 months. Therapy-induced reductions in pre- and afterload should, theoretically, decrease the stimulus for left ventricular hypertrophy further.[42] Moreover, decreased preload could have influenced echocardiographically measured systolic function according to Starling's law. However, this effect should have been balanced by the lower SBP found in affected dogs.

Results of our study are in agreement with the suggested hypothesis that decreased contractile performance may be an intrinsic property of left ventricular volume overload induced by naturally occurring CMVI in both SB and LB dogs, and that this decreased systolic function could be in part because of an inadequate degree of hypertrophy.

## Footnotes

[a] Ultrasonic Doppler Flow detector model 811-B, Parks Medical Electronics, Alhoa, OR

[b] MEGAS, ESAOTE Biomedica, Florence, Italy

[c] Instat 306, GraphPad Software, Inc., SanDiego, CA

[d] Borgarelli M, Crosara S, Savarino P, et al. Echocardiographic evaluation of systolic function in small and large breed dogs Proceed. Società Italiana delle Scienze Veterinarie (SISVet), Viareggio September 21–24 2005, 86 (abstract)

[e] Falk T, Jonsson L, Olsen LH, Pedersen HD Arteriosclerotic changes in myocardium, lung and kidney in dogs with chronic congestive heart failure and myxomatous mitral valve disease. J Vet Int Med 2005;19:932 (abstract)

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