Diagnostic value of echocardiographic indices of left atrial and ventricular morphology in dogs with myxomatous mitral valve disease (MMVD)

R. M. Trofimiak, L. G. Slivinska

Abstract

Myxomatous mitral valve disease (MMVD) is one of the most common acquired diseases of the cardiovascular system of genetic etiology in small breed dogs. A long asymptomatic course characterizes the disease. Presently, the main diagnostic technique for heart diseases is echocardiography. This study evaluates individual echoangiographic indices of the left atrial and ventricular morphology with the determination of the diagnostic value of each of them in predicting the course of the disease. The study was conducted in a private veterinary hospital “Eurovet” and on the basis of the clinic of the Department of internal animal diseases and clinical diagnostics of Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv during 2018–2019. The objects consisted of 46 dogs with a confirmed diagnosis of myxomatous mitral valve disease according to the recommendations of the American College of Veterinary Internal Medicine (ACVIM) and no signs of comorbidities. During the study, three experimental groups of animals were formed according to the clinical and functional status characteristic of each stage of MMVD development – B1, B2, C. According to the results, all experimental dogs showed changes in the mitral apparatus in the form of thickening of the anterior and posterior cusps, mitral valve (MV) prolapse into the left atrial (LA) cavity and regurgitation (MR), the severity of which increased with the stage of the disease (from 20 % to 60 %). In 44.4 % of animals in group B2, thickening of the left ventricular walls was diagnosed in diastole and in 22.2 % in systole. Instead, these values increase to 46.1 % and 53.8 % in group C, respectively. However, the degree of hypertrophy is disproportionate. With the development of the disease, we detect its decrease from 0.64 ± 0.03 (group B1) to 0.50 ± 0.04 (group B2) and 0.51 ± 0.03 (group C) also we observed an increase in LVEDD from 1.30 ± 0.05 cm (group B1) to 1.46 ± 0.12 cm (group B2) and 1.54 ± 0.13 cm (group C). The value of nLVEDD in B1 was 1.36 times (P < 0.001) lower compared to B2 and C. Higher values of this parameter were found in 23.1 % of dogs in group C compared to the maximum value of B2. As MV insufficiency progresses, the LA/Ao index increases slightly (1.08 times) in B2, followed by an increase in C (1.38 times, P < 0.001). At the same time, we diagnose an increase (P < 0.05) in PV/PA by 1.18 times in B2 and 1.46 times (P < 0.001) in C. Thus, an increase in the severity of mitral regurgitation, a rapid increase in nLVEDD, the dynamics of the decrease in the degree of hypertrophy h/R, as well as an increase in LA/AO, PV/PA indices are predictors of unfavorable prognosis of myxomatous degeneration of the mitral valve in dogs.

Key words: mitral regurgitation, myxomatous mitral valve disease, echocardiography, dog, volume overload.

1. Introduction

Atrioventricular valve endocardiosis occurs in 75 % of cases of acquired cardiovascular diseases of dogs (Borgarelli & Buchanan, 2012; Lopez-Alvarez et al., 2015; Merveille et al., 2015; Ramirez et al., 2016). According to various authors (Fox, 2012; Borgarelli & Buchanan, 2012; Chetboul & Tissier, 2012), the proportion of myxomatous mitral valve (MV) degeneration is 14–62 % (Yudina & Rybko, 2019; Keene et al., 2019), and the incidence and progression are closely related to age, breed, and sex (Fox, 2012; Borgarelli et al., 2004). According to studies (Fox, 2012; Borgarelli & Buchanan, 2012; Chetboul & Tissier, 2012; Sargent et al., 2015; Keene et al., 2019; Morgan et al., 2020), this disease is characterized by degenerative changes in the mitral appa-
changes by echocardiography (Chetboul & Tissier, 2012; Toaldo et al., 2016). A positive correlation was established between the severity of mitral valve prolapse and the degree of regurgitation with increasing CHF class (ISACHC class). Evaluation of the latter is important because it directly reflects the hemodynamic result of incomplete coaptation of the MV cusps during systole (Chetboul and Tissier, 2012). Such indicators of systolic function as fractional shortening (FS) and ejection fraction (EF) with the MMVD progression from ISACHC I to ISACHC III class remain within the reference range of 30–49 % and 55–75 %, respectively (Borgarelli et al., 2007; Chetboul & Tissier, 2012). The severity and incidence of pulmonary hypertension (PH) also increase with the MMVD progression (prevalence of 27 % ISACHC I, 72 % ISACHC III). However, it should be noted that it can be detected in the early stages of the disease (ISACHC Ia, ISACHC Ib) if moderate to severe MR accompanies MMVD (Chetboul & Tissier, 2012; Reynolds et al., 2012). The development of PH is a prognostic factor for survival in dogs with MMVD symptoms, as well as a sign of increased decompensation in asymptomatic animals (Chetboul & Tissier, 2012).

At present, such issues as monitoring technique, predicting the course of MMVD, expansion of risk stratification schemes remain controversial. Therefore, the study aimed to evaluate the echocardiographic indices of left atrial and ventricular morphology, as well as to establish their diagnostic value in the MMVD progression in dogs.

2. Materials and methods

The study was conducted in a private veterinary hospital “Eurovet” and on the basis of the clinic of the Department of internal animal diseases and clinical diagnostics of Stepan Gzhyskyi National University of Veterinary Medicine and Biotechnology Lviv during 2018–2019. The study included 46 dogs with mitral valve endocardiosis. The diagnosis was confirmed according to the criteria recommended by the American College of Veterinary Internal Medicine (ACVIM) (weight < 20 kg, left apical murmur, thickening and/or prolapse of MV leaflets in 2D mode, the presence of MR by color flow mapping (CFM), FS > 20 %, EF > 40 %) (Keene et al., 2019) and no signs of comorbidities. During the study, three experimental groups of animals were formed according to the clinical and functional status characteristic of each stage of MMVD development – B1 (group B1), B2 (group B2) and C (group C) (according to the ACVIM classification). Group B1 consisted of 25 animals (10 males, 15 females), age range was 7–14 (10.9 ± 0.47) years, body weight was in the range of 3.14–17.5 (8.4 ± 0.86) kg, the most common breeds were English Cocker Spaniel, mixed breed dogs, Yorkshire Terrier, Dachshund, Chihuahua, Maltese, Miniature Pinscher, Papillon, Pug. Group B2 included 9 animals (6 males, 3 females) aged 7–18 (11.1 ± 1.22) years and weighing 1.7–9.85 (4.8 ± 0.89) kg, among breeds were Pekingese, Dachshund, mixed breed dogs, Yorkshire Terrier, Chihuahua, Maltese. Group C included 12 dogs (6 males, 7 females), age ranged from 8–15 (11.8 ± 0.66) years, and body weight – 1.9–10.5 (5.3 ± 0.77) kg, breeds – Pekingese, Yorkshire Terrier, Miniature Schnauzer, mixed breed dogs, Dachshund, Miniature Poodle, Beaver Yorkshire Terrier. Transthoracic echocardiographic examination using 2 D, M-modes, pulse-wave (PW) Doppler, as well as color flow mapping (CFM) was performed with Siemens (Acuson) S2000 and Esaote MyLab 40 equipped with a 4–10 MHz and a 5–8.5 MHz phased-array transducers, depending on the size of the animal. One ECG lead was recorded at a time. Fixation of animals was performed without the use of sedative pharmacological agents in the right and left lateral positions on a table with a cutout. Before the examination, the dogs were sheared in the sternal area and at the level of the costochondral junctions on both sides of the chest, and the skin surface was degreased with 70° ethanol, followed by a layer of acoustic gel.Qualitative images obtained from standardized projections were used to visualize cardiac structures and perform measurements (Thomas et al., 1994). The control data were the literature reference echocardiographic normal values according to the bodyweight of the object under study (Boon, 2017). For 2D-assessment of MV morphology (thickening, prolapse), the right parasternal four-chamber long axis view and the left four-chamber apical axis view were derived, and CFM-mode was used to detect and semi-quantitatively assess (ARJ/LAA) the MR degree (Chetboul & Tissier, 2012). LV measurements in systole and diastole: interventricular septum (IVS), LV end-systolic dimension (LVESD), LV end-diastolic dimension (LVEDD), left ventricular posterior wall (LVPW) were determined using M-mode in the right parasternal short axis view at the level of papillary muscles, followed by indexation of LVESD, LVEDD according to body weight for a reliable assessment of cardiac remodeling (Cornell et al., 2004). The degree of hypertrophy was determined using the ratio h/R, where h is the thickness of LVPWd, and R = LVEDD/2 (Borgarelli et al., 2007). The ratio LA/Ao was calculated from the measurements obtained in the right parasternal short axis view at the level of the aortic root in diastole, and PV/PA – the ratio of the pulmonary vein (PV) to the right branch of the pulmonary artery (PA) obtained in the right parasternal four-chamber long axis view at the end of the T wave. End-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction were determined by a modified Simpson method. Five cardiac cycles were evaluated to derive the mean for each parameter. All calculations were performed with a PC, mathematical processing of the results was performed using Microsoft Office Excel 2010 software according to the generally accepted methods of variation statistics, with an estimate of the mean value (M), its margin of error (m). The significance was determined by Student's t-test.

3. Results and discussion

Results

According to the anamnesis and clinical examination, groups B1 and B2 included animals in which no symptoms of the disease were detected at the time of the study. At auscultation of dogs in group B1, the left apical systolic murmur with the intensity of 1/6–2/6 was registered in 37 % of cases. In group B2, the prevalence of this type of murmur was 75 %, and the intensity increased to 3/6–4/6, in contrast to group C – 95 % with an intensity of 4/6–5/6, respectively. According to the results of the clinical study, the following was found in animals of the experimental group C: anemia of mucous membranes (61.5 %), cyanosis (15.4 %), increased CRT (84.6 %), positive expiration reflex and coughing (69.2 %), contouring of jugular veins (46.2 %), tachypnea (76.9 %), tachycardia, prolonged noisy expiration
fine moist rales (53.8 %), increase in abdominal volume (38.5 %).

Changes in the mitral apparatus were diagnosed in all studied animals. In group B1, thickening of the anterior cusp (80 %), posterior (4 %), and both cusps (16 %), mild MR (ARJ/LAA < 20 %) have been detected. MV prolapse into the left atrial cavity was registered in 28 % of dogs. In group B2, the thickening of the anterior, both cusps were found in 71 % and 29 %, respectively. There were moderate MR (ARJ/LAA ≥ 20–40 %) and signs of remodeling (hypertrophy of the left ventricular walls, LV chamber dilatation and LA enlargement). The direction of the regurgitation flow was lateral. In dogs of group C, MV changes are characterized by thickening of the anterior (46.2 %), posterior (7.6 %), and both cusps (46.2 %). MV prolapse (30.1 %) and posterior cusp prolapse (7.7 %) were established. Moderate MR (ARJ/LAA ≥ 30–60 %) with hemodynamic effects of LA volume overload. The direction of MR flow is lateral (92.3 %) and medial (7.7 %).

The main echocardiographic parameters of LV measurements are given in table 1. According to the assessment results of LV walls thickness in the systolic and diastolic phases, changes were found in each experimental group. We register a slight increase in IVSd, LVPWd, without changes in the values of IVSs and LVPWs in 20 % of B1 animals. In contrast, the number of B2 dogs with a moderate increase in diastolic measurements of LV walls thickness increases to 44.4 %. An increase in the thickness of IVS and LVPW in the systolic phase is recorded in 22.2 %. In group C, 46.1 % of dogs showed thickening of the LV walls during diastole, and 53.8 % – during systole.

In addition to determining the thickness of the walls, attention was also paid to the study of the degree of their hypertrophy with the MMVD progression. The results are presented in the form of diagram (Fig 1).

**Table 1**

Echocardiographic parameters of the left ventricle (M-mode) in dogs of experimental groups with the progression of MMVD

| Echocardiographic parameters | Biometric indicator | Experimental group of animals |
|-----------------------------|---------------------|------------------------------|
|                            | Biometric indicator | B1 (n = 25) | B2 (n = 9) | C (n = 13) |
| IVSd, cm                   | Lim                 | 0.43–1.11  | 0.46–0.97  | 0.46–1.15  |
|                            | M ± m               | 0.7 ± 0.03 | 0.7 ± 0.06 | 0.7 ± 0.05 |
| LVEDD, cm                  | Lim                 | 1.6–3.55   | 2.1–4.24   | 1.48–4.89  |
|                            | M ± m               | 2.6 ± 0.10 | 2.9 ± 0.23 | 3.1 ± 0.26 |
| nLVEDD, cm/kg              | Lim                 | 1.13–1.69  | 1.71–2.18  | 1.06–2.54  |
|                            | M ± m               | 1.4 ± 0.03 | 1.9 ± 0.06** | 1.9 ± 0.10°°° |
| LVPWd, cm                  | Lim                 | 0.51–1.15  | 0.48–1.20  | 0.55–1.06  |
|                            | M ± m               | 0.8 ± 0.04 | 0.7 ± 0.07 | 0.8 ± 0.05 |
| IVSs, cm                   | Lim                 | 0.71–1.94  | 0.76–1.52  | 0.74–1.52  |
|                            | M ± m               | 1.1 ± 0.06 | 1.0 ± 0.08 | 1.1 ± 0.06 |
| LVESD, cm                  | Lim                 | 0.92–1.98  | 1.11–2.23  | 0.65–2.91  |
|                            | M ± m               | 1.4 ± 0.05 | 1.7 ± 0.11 | 1.4 ± 0.17 |
| nLVESD, cm/kg              | Lim                 | 0.52–1.00  | 0.87–1.70  | 0.45–1.45  |
|                            | M ± m               | 0.7 ± 0.02 | 1.1 ± 0.08*** | 0.9 ± 0.07° |
| LVPWs                      | Lim                 | 0.8–1.66   | 0.81–1.8   | 0.89–1.88  |
|                            | M ± m               | 1.2 ± 0.05 | 1.2 ± 0.11 | 1.3 ± 0.07 |

**Note:** **– P < 0.001 – significant difference compared to the parameters of group B1, ° – P < 0.05 – significant difference compared to the parameters of group B1, °°° – P < 0.001 – significant difference compared to the parameters of group B1

**Fig. 1.** Box and whisker plot showing the radius of the LV cavity in diastole (R) and the ratio of the thickness of LVPWd (h) to R in dogs of experimental groups with the progression of MMVD with indication of limits.
In sick dogs, the radius of the LV cavity in diastole increases according to the progression of the MMVD stages from 1.30 ± 0.05 cm (group B1) to 1.46 ± 0.12 cm (group B2) and 1.54 ± 0.13 cm (group C). At the same time, the degree of walls thickening with the development of the disease decreases from 0.64 ± 0.03 (group B1) to 0.50 ± 0.04 (group B2) and 0.51 ± 0.03 (group C).

The analysis of the nLVEDD value in sick dogs revealed its probable changes. Thus, this indicator was 1.36 times (P < 0.001) lower in B1 animals compared to groups B2 and C, while in groups B2 and C a probable difference between the values was not found. However, higher nLVEDD values were found in 23.1 % of the experimental group C dogs compared to the maximum value in group B2.

Similar changes were found when evaluating the nLVESD values. It is increased by 1.57 (P < 0.001) and 1.29 (P < 0.05) times in experimental dogs of groups B2 and C, respectively, compared with the same indicator in group B1. When compared the values in groups B2 and C were approximate and did not differ statistically. This indicator is within the reference range in all three groups (1 ± 0.1 cm/kg).

A study of end-systolic volume index (ESVI) values (Fig. 2) and functional parameters such as FS, EF (Fig. 3, 4) was also performed in the experimental groups of animals. The ESVI value in experimental group B1 was within the reference range (< 30 ml/m2). In group B2, we noted its increase (P < 0.001) in 1.97 times and in 33.3 % of dogs this determinant is higher than the upper limit value. At the same time, ESVI increases 1.61 times in group C compared to B1 and it is 1.22 times lower than in group B2.

The FS index in group B1 was in the range of 32–61 % and averaged 42.6 ± 1.16 % at the reference range of 30–47 % (Fig. 3). Its increase was registered in 32 % of dogs. Similar changes are observed in group B2. The mean FS value was 44.3 ± 1.97 %, and an increase was found in 33.3 % of experimental animals. The value of FS increases above normal in 76.9 % of dogs and averages 54.0 ± 3.02 % in group C in contrast to the other two experimental groups.

When estimating EF (Fig. 4) we found that the values of this parameter are higher than the norms (55–76 %) in group B1 (76.8 ± 1.67 %) and B2 (76.6 ± 1.97 %) and they are approximately the same. Alongside this, the EF value increases to 81.9 ± 3.45 % in group C.

The LA/Ao ratio in dogs with MMVD progression was also evaluated (Fig. 5).

This index was in the range of 1.02–1.42 (1.2 ± 0.02) in group B1, which corresponded to the reference values (1–1.6). With the progression of MV insufficiency, there is a slight increase of 1.08 times in group B2 and 1.38 times (P < 0.001) in group C.

In addition to the assessment of the LA to Ao ratio, an additional study of the ratio of pulmonary vein diameter (PV) to the diameter of the right branch of the pulmonary artery (PA) was conducted in three experimental groups (Fig. 6).
Fig. 3. Spot diagram of the FS values of experimental animals with the progression of MMVD

Fig. 4. Spot diagram of the EF values of experimental animals with the progression of MMVD
According to the obtained results, this indicator was within the reference range (0.8–1.7) in the first group of animals and averaged 1.1. We noted its increase ($P < 0.05$) in 1.18 times in group B2, but the values (0.9–1.6) did not exceed the reference limits. In group C, the ratio of PV/PA continued to increase ($P < 0.001$) and in 61.5% of animals exceeded the reference values. We found a simultaneous proportional increase in LA/Ao and PV/PA with the MMVD progression (Fig. 6).

**Discussion**

Analyzing the age range of animals in the experimental groups, a clear increase in the mean value of age with the progression in the class of heart failure (HF) is observed, which is consistent with the literature. The cause of holosystolic left apical murmur in dogs is the presence of regurgitation blood flow in LA during systole. The development of clinical symptoms in animals of experimental group C is the result of the stage of decompensation, which is characterized in MMVD by a critical increase in preload, retrograde hemostasis in the pulmonary circulation, and the development of right heart failure with further progression. One of the links in the pathogenesis of MMVD is the presence of MR. It was found that even a semi-quantitative assessment of the general appearance of the regurgitation jet (size and depth of penetration into LA), as well as the morphology of MV, has prognostic value because the volume overload of the left heart increases with the progression of the above indicators associated with the appearance of clinical symptoms and deterioration of the HF class (Sargent et al., 2015; Larouche-Lebel et al., 2019).

An increase in nLVEDD values along with normal values or thickening of IVS and LVPW indicates remodeling of the LV cavity in the form of eccentric hypertrophy. The latter occurs due to MR, followed by an increase in volume overload with the HF progression in MMVD (Reynolds et al., 2012; Chetboul & Tissier, 2012; Ramirez et al., 2016). According to the results of the study, it should be noted that...
a rapid increase in nLVEDD occurs immediately before the
decompensation stage, i.e. in the experimental group B2
(Chetboul & Tissier, 2012). The values of nLVEDD and LV
walls size in systole comprise the criteria for assessing myo-
cardial contractile function, and therefore the presence of
these values within normal limits indicates the preservation
of contractility.

The change in LV walls thickness due to remodeling oc-
curs according to Laplace’s law, which helps to normalize the
load on the wall during systole, but not during diastole
(Borgarelli et al., 2007). In the settings of a progressive
increase in chamber size due to volume overload during
prolonged MR, we do not observe a corresponding directly
proportional increase in wall thickness. Thus, the LVPW
thickness in sick dogs does not differ significantly from
animals in the preclinical stages, but their radius of the LV
cavity is much larger, which reduces the h/R value. This fact
has an unfavorable prognostic value because there will be a
deterioration in systolic function in the later HF stages.

Such echocardiographic determinants as ESVI, FS, and
EF are indicators of myocardial systolic function. According
to the literature (Borgarelli et al., 2007; Chetboul & Tissier,
2012; Ramírez et al., 2016), we find differences in the opin-
ion of the authors regarding the contractility of the heart
muscle. According to the results of studies (Borgarelli et al.,
2007; Chetboul & Tissier, 2012; Sargent et al., 2015; Ramí-
rez et al., 2016; Rudenko, 2018), there is a gradual
increase in FS and EF in dogs with the MMVD progression
and at first glance, it indicates not only the preservation of
systolic capacity but also its increase. Such positive dynam-
ics represents the method of calculating these indices. FS
and EF calculations depend on afterload, which is explained
by a decrease in systolic and diastolic blood pressure
(Ramírez et al., 2016), and preload, which increases with
increasing degree of MR with the MMVD progression
(Chetboul & Tissier, 2012; Sargent et al., 2015). Moreover,
due to MV deficiency, an additional retrograde blood flow to
the heart chamber with less resistance (left atrium) is
created, which occurs faster than the opening of the aortic
valve (Chetboul & Tissier, 2012). The hyperkinesis of IVS
and LVPW seems to play also an important role in the
growth of these functional parameters. Taking into account
the above-mentioned facts, as well as the ESVI increase in
sick dogs of groups B2 and C, we can conclude that the
MMVD progression does reduce the true contractility of the
LV myocardium, which is compensated at these stages by
activation of the sympathetic-adrenal system and Frank-
Starling mechanism.

Given the fact that the experimental groups included
dogs with different body weights, in this study, we used the
index of the LA/Ao ratio to estimate the LA size (Chetboul
& Tissier, 2012). Its increase with each MMVD stage
indicates an enlargement of the LA chamber due to volume
overload, which occurs due to chronic and hemodynamically
significant MR. It should be emphasized that in the initial asymptomatic stage, this phenomenon has
a compensatory value because it prevents the development of hemostasis in the pulmonary circulation due to increased
reserve capacity of LA. However, with further progression of
the disease, subsequent dilatation of LA leads to a
decrease in its functions (conductive, contractile) with
retrograde hemostasis and the manifestation of clinical
symptoms. Thus, LA enlargement is a negative prognostic
sign in animals with MMVD (Schober et al., 2010; Chetboul
& Tissier, 2012; Hollmer et al., 2017; Toaldo et al., 2018).
An additional parameter for indirect assessment of pressure
increase in LA is the size of the pulmonary vein diameter,
which is determined by the following PV/PA ratio. The
growth of the latter indicates a relative expansion of the
vessel lumen due to increased pulmonary venous pressure,
which in turn is a retrograde consequence of the increase in
the LA pressure. The development of pulmonary venous
stasis is a negative prognostic sign, which is a trigger factor
for the development of pulmonary edema. Simultaneous
direct proportional growth of LA/Ao and PV/PA with
MMVD progression was also found. Thus, according to the
results of our studies, the ratio of PV/PA is a predictor of the
development of heart failure in dogs with MMVD with a
sensitivity of 96 % and a specificity of 91 % (Merveille et
al., 2015).

4. Conclusions

During the echocardiographic examination of dogs with
MMVD at different stages, we found that the increase in the
severity of MR, the rapid increase in nLVEDD, the tendency
of decreasing h/R, as well as increase of LA/AO, PV/PA
indices are predictors of unfavorable prognosis of MMVD
in dogs. Evaluation of such echocardiographic determinants
as ESVI, FS, and EF had no significant prognostic value in
the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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