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Evaluation of an echocardiogram in the preclinical stage of valve endocardiosis in dogs using an angiotensin converting enzyme inhibitor and an aldosterone antagonist

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ABSTRACT

The article presents the results of a study of the dynamics of ultrasonographic changes in dogs with endocardial atrioventricular valve endocardiosis during therapy with an angiotensin converting enzyme inhibitor and aldosterone antagonist. The authors also propose a new method for estimating the cubic volume of the left atrium based on the "area-length" method borrowed from humane medicine and correlation with the routine estimation method for measuring the size of the aorta and left atrium with further calculations of the dynamic index for assessing the remodeling processes. It has shown that the appearance of diastolic dysfunction by the type of slowing down the relaxation of the transmitral flow in the left apical four-chamber projection characterized by a decrease in the ratio of early diastolic filling (peak E) and filling due to systole of the left atrium (peak A) and an increase in the time of early diastolic filling (DTE) were determined at the beginning of the disease. However, changes in the trans mitral diastolic flow after 6 months took the form of "pseudonormalization", which was seen in the Dopplerogram as normalization of the ratio of early diastolic filling (peak E) and an increase in filling due to left atrial systole (peak A) and time of early diastolic filling (DTE). After 12 months of therapy, the diastolic flow through the mitral valve in the Group 1 and partly in the Group 2 became "restrictive", characterized by an increase in the ratio of early diastolic filling (peak E) and filling due to systole of the left atrium (peak A) and a decrease in the time of early diastolic filling (DTE). However, the authors found that the appearance of diastolic dysfunction, an increase in the left atrium and a dynamic remodeling index directly correlate with the onset of the clinical manifestation of endocardiosis.

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INTRODUCTION

Endocardiosis is a chronic, degenerative lesion of the heart valves, in which changes in collagen and elastin fibers occur, which leads to the formation of nodules along the edges with further thickening and scar deformation (Ahamed *et al.*, 2019). It is known that the initial manifestation of the disease is not clinically expressed. However, at the initial stage, a number of changes take place in the heart, in particular, remodeling of the left atrium with mitral insufficiency, which subsequently leads to the appearance of the most important clinical

sign of the disease: cough. The latter occurs due to compression of the left main bronchus by an enlarged atrium (Atkins *et al.*, 2007; Pouchelon *et al.*, 2008). But the speed of development of this process remains in question. From literature, it is known that aldosterone promotes the retention of water and sodium and thereby increases the volume of extracellular fluid, leading to an increase in cardiac preload (Dmitriyevich *et al.*, 2016). However, according to some authors, aldosterone has a direct effect on the myocardium and vascular endothelium (Egorov *et al.*, 2018). It should also be noted that the therapeutic efficacy of angiotensin-converting enzyme inhibitors and aldosterone antagonists at the preclinical stage has been little studied. At present, there is no general opinion of experts about the time of initiation of therapy for endocardiosis of atrioventricular valves Farquharson and Struthers (2002); Pu *et al.* (2003). Ultrasonographic examination of the heart leaves unclear questions regarding changes in the volume of the left atrium during mitral regurgitation. To date, echocardiography specialists routinely apply a method for assessing changes in the size of the left atrium with respect to the aorta. It is no secret that ultrasonography of the heart is a subjective diagnostic method and in some cases errors associated with the operator are detected in measuring these parts of the heart, so we borrowed a method for measuring the cubic volume of the left atrium from human medicine (Jinu *et al.*, 2018) and developed a unified index to evaluate remodeling. Thus, today, the question of changing the echocardiographic parameters of dogs with endocardiosis of atrioventricular valves at the preclinical stage remains debatable.

In this regard, we set the following goal: to conduct an echocardiographic study of animals and conduct a dynamic assessment of the developed authors' index of changes in the left atrium, due to cubic volume by the area-length method (Khristoforovich *et al.*, 2016; Semenov *et al.*, 2018), as well as to evaluate the therapeutic efficacy of Vazotop and Verospiron preparations for the pathology under discussion.

MATERIALS AND METHODS

The work is based on the results of studies conducted in the period from 2016 to 2019 on the basis of the Department of Animal Diseases of the Saratov State Agrarian University and veterinary clinics of Little Raccoon (cities of Pushchino, Serpukhov, Moscow Oblast).

The subject of the study was the therapeutic efficacy of the Vazotop angiotensin converting enzyme inhibitor (active substance of ramipril) and the aldosterone antagonist of Verospiron (active substance spironolactone) in the treatment of dogs with preclinical endocardial atrioventricular valves**.** The object of the study was 75 dogs in a preclinical stage of endocardiosis of atrioventricular valves. The animals were of various breeds aged from 2 to 10 years with a live weight from 2 to 15 kg.

Material for the study was blood and its serum of sick animals, ultrasonograms, electrocardiograms, thoracic radiograms, and outpatient admission journals. The following research methods were used in work: clinical, biochemical, electrocardiographic, ultrasonographic, radiographic, statistical.

During treatment, all animals were divided into 3 groups of 25 animals each. During the experiment, all dogs were transferred to a low sodium (Royal Canin Cardiac) treatment feed. In this case, the dogs of Group 1 served as reference ones. In addition to therapeutic feed, nothing else was prescribed to them. Animals of the Group 2 received therapeutic food and an inhibitor of the Vazotop angiotensin converting enzyme at a dose of 0.125 mg per 1 kg of animal weight once a day for 12 months. Dogs of Group 3 also received therapeutic food, an inhibitor of the Vazotop angiotensin converting enzyme at a dose of 0.125 mg per 1 kg of animal weight once a day for 12 months and an aldosterone antagonist of Verospiron at a dose of 1 mg per 1 kg of animal weight once a day for 12 months.

Blood for biochemical and clinical studies in animals was aspirated from a forearm vein or a Safen vein on an empty stomach in a volume of 5 ml into a test tube with a coagulation activator for biochemical research and with EDTA for clinical analysis. Blood serum was studied on an Idexx Catalyst One device (USA). Blood with EDTA – on a Mindray BC-3100 automated hematology analyzer (China). Reference values were the data from the veterinarians' manual (Kvart *et al.*, 2002).

Electrocardiograms were recorded on a Biokare (China) electrocardiograph. In leads I, II, III, standard and reinforced aVR, aVL and aVF derived from extremities. ECG interpretation was carried out by the accepted methods of measuring and calculating the height of peaks and intervals, heart rate, heart axis and pacemaker using a special electrocardiographic ruler of V. Lyusova and N.A. Kozinsky, commissioned by the GEOTAR-Media Publishing Group (Aafreen *et al.*, 2018).

X-ray diffraction study was performed on DIAGNOSTIC X-RAY Roentgen diagnostic unit (China). For work, we used the Carestream X-ray Green film,

which was placed in a special X-RAY cassette. The exposed film was developed by standard radiological methods.

Echocardiography was performed on a Mindray Z5 Vet unit (China) using a phased sensor with a frequency of 5-7.5 MHz. In this case, measurements were made of the sizes of the left and right ventricles, left and right atria, aorta, pulmonary artery, thickness of the posterior wall of the left ventricle and interventricular septum, the state of the valve apparatus, flow rates (mitral, tricuspid, transaortic, and transpulmonary) were estimated in standard projections (left and right parasternal) using the B-, M-modal, Doppler mode (pulse-wave, constant-wave and color Doppler flow mapping). The calculated contractility fraction was obtained by the formula of Teicholz:

$$CF = \frac{LVEDd - LVESD}{LVESD} * 100\%$$

where CF is the contractility fraction; LVEDd – left ventricular end-diastolic dimension, measured in the M-modal mode of the right parasternal projection at the level of the ends of the cusps of the mitral valve; LVESD – left ventricle end-systolic diameter.

The ejection fraction index was calculated using the Simpson automated modified disc method. The ratio of the sizes of the left atrium to the aortic valve (LA/Ao) was determined by calculation. Also, the average pressure in the pulmonary artery was determined by the ratio of the time of acceleration of the flow in the outflow tract of the right ventricle (AT) to the ejection time (ET). The degree of mitral regurgitation was assessed using Doppler mapping, through the percentage of the return flow to the area of the left atrium. Also, the E-peak deceleration time (DTE), mitral flow velocity in early diastole (VE), and mitral flow velocity at atrial contraction (VA) and their ratio. The volume of the left atrium was determined by the area-length method used to determine the volume of the left ventricle, which is used in humane medicine (Matveeva *et al.*, 2015). Received volumes before treatment at further observation were divided into volumes after 6 and 12 months of therapy. As a result, we got an index, which, in our opinion, evaluated the processes of remodeling of the left atrium. If the index was 1±0.1, then we evaluated it as normal, that is, there were no remodeling processes. If the index was less than 1, then this, in our opinion, indicates remodeling of the left atrium.

Clinical, hematological, biochemical electrocardiographic, radiological, and ultrasonographic studies were performed on the day patients were received for treatment, as well as after 6 and 12 months of supervision.

RESULTS AND DISCUSSION

Prior to the start of therapy, the results of echocardiography in B- and M-modes in the right projection along the long axis in all animals in all groups noted the presence of changes in the mitral valve, the cusps of which were deformed and thickened. Along the short axis in the right parasternal projection, at the level of the aortic valve, eccentric hypertrophy of the left atrium and normal aortic valve correlated with animal weight was observed in all animals, in all the groups studied. Left atrium to the aorta ratio index in Group 1 was 1.3 ± 0.2 cu, in Group 2 – 1.5 ± 0.1 cu, in Group 3 – 1.4 ± 0.1 cu, which determined the presence of dilatation of the left atrium (Figure 1).

Pulmonary hypertension was not diagnosed in any animal. In the left parasternal projection in a four-chamber section, an altered mitral valve, the cusps of which were thickened, mobile, and deformed, was noted. When using constant-wave Dopplerometry, a laminar flow was detected with early diastolic (peak E), and early systolic (peak A) left ventricular filling velocity in Group 1 – 0.8±0.1 cu, in Group 2 – 0,7±0.2 cu, Group 3 – 0.8±0.1 cu, which corresponded to the "relaxation deceleration" type diastolic dysfunction (Figure 2).

Also in this projection and along this section, a regurgitant flow was located through the mitral valve into the cavity of the left atrium, calculated by the percentage of the jet area and the area of the left atrium, with color Doppler mapping in Group 1 in 32±1.2%, in Group 2 – 29±1,5%, in Group 3 – 31±1.7, which corresponded to all animals having the II degree mitral regurgitation (moderate). Deceleration time of early diastolic left ventricular filling (DTE) was 253±2.1 m/s in Group 1, 248±2.6 m/s in Group 2, and 267±2.3 m/s in Group 3, which also confirmed "delayed relaxation" type diastolic dysfunction of the left ventricle (Figure 3).

The tricuspid valve in 1 animal of Group 1, 1 animal of Group 2 and 1 animal of Group 3 (4.0%) was changed, the cusps are deformed, thickened and discordant, with tricuspid regurgitation of the 1st degree (less than 20.0% by the ratio of the jet area to the area of the right atrium), in the remaining animals (96.0%), the valve was located without changes, the cusps were defined as thin, not thickened. In the remaining 72 (96.0%) animals, laminar flow without regurgitation was determined at an average speed with an early diastolic peak (E) of 0.7±0.2 m/s in Group 1, 0.5±0.1 m/s in Group 2, 0.8±0.1 m/s in Group 3.

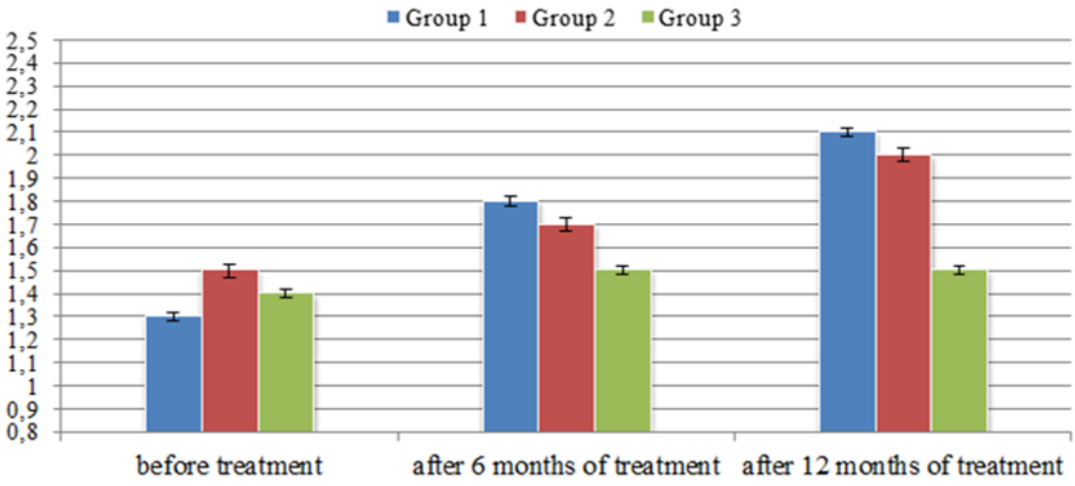

Figure 1: Dynamics of changes in the ratio of the left atrium to the aorta in the treatment of dogs suffering from endocardiosis of atrioventricular valves at the preclinical stage

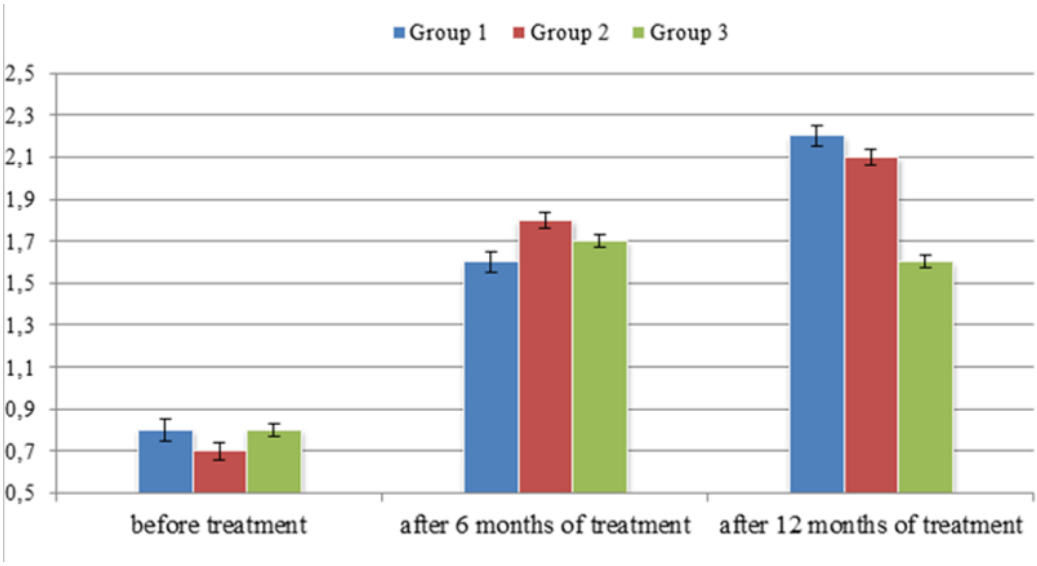

Figure 2: Dynamics of changes in the ratio of E/A transmitral flow in the treatment of dogs suffering from endocardiosis of atrioventricular valves at the preclinical stage

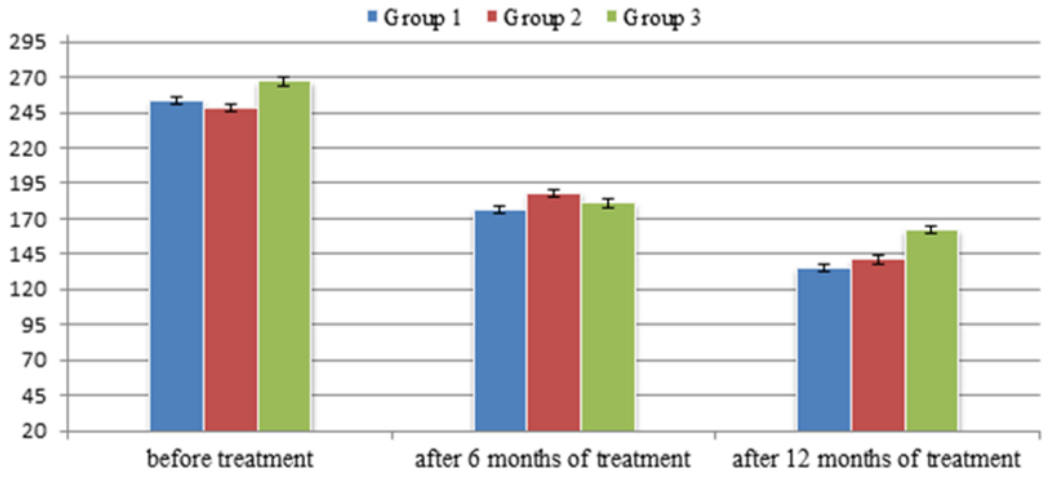

Figure 3: Dynamics of changes in the time of early diastolic filling of the left ventricle (DTE) in the treatment of dogs suffering from endocardiosis of atrioventricular valvesat the preclinical stage

The remaining parameters determined according to the study scheme (the sizes of the cavity of the right ventricle and the right atrium, pulmonary artery, the thickness of the posterior wall of the left ventricle and interventricular septum, the state of the valve apparatus, the (tricuspid and transaortic) flow rate of ejection fractions according to the Simpson disc method) were within the reference quantities.

Also, to control the dynamics of remodeling according to the author's method, measurements were made of the left atrium volume in the right parasternal projection in the short axis at the level of the aortic valve and the left parasternal projection in a four-chamber section, both in systole and in diastole, determining the volume of the cavity.

With control echocardiography after 6 months of therapy in B- and M-modes in the right parasternal projection along the long axis in all animals (100.0%) in all groups noted the presence of changes in the mitral valve, the cusps of which were deformed, thickened, mobile. Along the short axis in the right parasternal projection, at the level of the aortic valve, eccentric hypertrophy of the left atrium and normal aortic valve correlated with animal weight was observed in all animals, in all the groups studied. Left atrium to the aorta ratio index in Group 1 was 1.8 $\pm$ 0.2 cu, in Group 2 – 1.7 $\pm$ 0.1 cu, in Group 3 – 1.5 $\pm$ 0.3 cu, which determined the presence of dilatation of the left atrium. The transpulmonary laminar flow was determined, without regurgitation, with a speed and pressure gradient without changing the physiological norm in all animals. Pulmonary hypertension was not diagnosed in any animal.

In the left parasternal projection in a four-chamber section, an altered mitral valve, the cusps of which were thickened, mobile, and deformed, was noted. When using constant-wave Dopplerometry, laminar flow was located with early diastolic (peak E), and early systolic (peak A) left ventricular filling velocity in Group 1 – 1.6$\pm$0.1 cu, in Group 2 – 1,8$\pm$0.1 cu, Group 3 – 1.7$\pm$0.1 cu, which corresponded to the "pseudo normalization" type diastolic dysfunction. Also in this projection and along this section, a regurgitant flow was located through the mitral valve into the cavity of the left atrium, calculated by the percentage of the area of the jet and the area of the left atrium, with color Doppler mapping in Group 1 in 27$\pm$1.6%, in Group 2 – 32$\pm$1.2%, in Group 3 – 30$\pm$1.3, which corresponded to all animals having the degree II mitral regurgitation (moderate). Deceleration time of mitral flow velocity in early diastole (DTE) was 176.4$\pm$2.5 m/s in Group 1, 188.2$\pm$2.1 m/s in Group 2, and 181.2$\pm$2.2 m/s in Group 3, which also confirmed "pseudo normalization" type diastolic dysfunction of the left ventricle. The tricuspid valve in 1 animal of Group 1, 1 animal of Group 2 and 1 animal of Group 3 (4.0%) was still changed, the cusps were deformed, thickened and discordant with tricuspid regurgitation of the 1 degree (less than 20% by the ratio of the jet area to the area of the right atrium), in the remaining animals (96.0%), the valve was located without changes, the cusps were defined as thin, not thickened, and laminar flow without regurgitation was still determined at an average early diastolic filling velocity (E) of 0.8$\pm$0.2 m/s in Group 1, 0.6$\pm$0.1 m/s in Group 2, 0.8$\pm$0.1 m/s in Group 3.

The remaining indicators, determined according to the research scheme, were within the framework of reference values.

Also, to control the dynamics of remodeling according to the author's method, the volume of the left atrium was measured in the right parasternal projection in the short axis at the level of the aortic valve and the left parasternal projection in the four-chamber section, both in systole and in diastole, determining the volume of the cavity and calculating the dynamic index by calculation estimates of remodeling of the left atrium, which amounted to 0.84$\pm$0.1 cu in Group 1, 0.82 $\pm$ 0.1 cu in Group 2, and 1$\pm$0.1 cu in Group 3.

After 12 months of therapy with control echocardiography in B- and M-modes in the right parasternal projection along the long axis in all animals in all groups we noted the presence of changes in the mitral valve, the cusps of which were deformed, thickened, mobile. Along the short axis in the right parasternal projection, at the level of the aortic valve, eccentric hypertrophy of the left atrium and normal aortic valve correlated with animal weight was observed in all animals, in all the groups studied. Left atrium to the aorta ratio index in Group 1 was 2.1 $\pm$ 0.2 cu, in Group 2 – 2.0 $\pm$ 0.1 cu, in Group 3 – 1.5 $\pm$ 0.2 cu, which determined the presence of dilatation of the left atrium. As before, the transpulmonary laminar flow was determined without regurgitation, with a speed and pressure gradient that did not go beyond the reference values and the absence of pulmonary hypertension in all animals. In the left parasternal projection in a four-chamber section, an altered mitral valve, the cusps of which were thickened, mobile, and deformed, was noted. When using constant-wave Dopplerometry, a laminar flow was located with early diastolic (peak E), and early systolic (peak A) left ventricular filling velocity of 2.2$\pm$0.2 cu in Group 1, 2.1 $\pm$ 0.1 in Group 2, which corresponded to diastolic dysfunction of

the left ventricle according to the type of "restrictive flow"; in Group 3, "pseudonormalization" was still detected and the ratio was 1.6 ± 0.1 cu. Also, in this projection and along this section, a regurgitant flow was located through the mitral valve into the cavity of the left atrium, calculated by the percentage of the area of the jet and the area of the left atrium, with color Doppler mapping of 31 ± 1.8% in Group 1, 27±1.4% in Group 2, 31 ± 1.2% in Group 3, which was still consistent in all animals of the II degree of mitral regurgitation (moderate). Deceleration time of early diastolic filling of the left ventricle (DTE) was 135.1 ± 2.1 m/s in Group 1, 141.1 ± 2.5 m/s in Group 2, which also confirmed the "restrictive" type of left ventricular diastolic dysfunction, but in Group 3, "pseudo-normalization" was still recorded with a deceleration time of 162.2 ± 2.7 m/s. The tricuspid valve in 1 animal of Group 1, 1 animal of Group 2 and 1 animsl of Group 3 (4%) was still changed, the cusps were deformed, thickened and discordant with mitral regurgitation of the 1 degree (less than 20% by ratio of the jet area to the area of the right atrium), in the remaining animals (96.0%), the valve was located without changes, the cusps were defined as thin, not thickened, and laminar flow without regurgitation was still visualized at an average early diastolic filling velocity (E) of 0.7±0.2 m/s in Group 1, 0.8±0.1 m/s in Group 2, 0.7±0.1 m/s in Group 3.

Also, to control the dynamics of remodeling according to the author's method, the volume of the left atrium was measured in the right parasternal projection in the short axis at the level of the aortic valve and the left parasternal projection in the four-chamber section, both in systole and in diastole, determining the volume of the cavity and calculating the dynamic index by calculation estimates of remodeling of the left atrium, which amounted to 0.79±0.1 cu in Group 1, 0.77 ± 0.1 cu in Group 2, and 1±0.1 cu in Group 3.

CONCLUSION

According to the results of the study, when analyzing echocardiograms with mitral regurgitation as a result of mitral valve endocardiosis at the preclinical stage, we noted eccentric left atrial hypertrophy, which was diagnosed during the entire study in all animals by the indicators of the ratio of the left atrium to the aorta. At the beginning of therapy, diastolic dysfunction of the left ventricle was noted in all animals in all groups as "relaxation deceleration", which was clearly expressed in an increase in the atrial filling fraction (peak A), that is, according to the Frank-Starling law, a significant part of the diastolic flow was carried out in the phase of systole of the left atria.. Dopplerograms clearly showed a decrease in the E/A ratio of the transmitral flow below 1.0 cu, and an increase in the time of early diastolic filling (DTE) of more than 220 m/s. In the course of therapy, after 6 months, in all groups, diastolic dysfunction of the left ventricle acquired the type of "pseudonormalization", as evidenced by the normalization of the ratio of E/A peaks and the time of early diastolic filling. After 12 months, in Groups 1 and 2, diastolic dysfunction acquired the form of "restrictive" one, as evidenced by an increase in the ratio of E/A peaks of more than 1.6 cu, and a decrease in DTE of less than 160 m/s, in contrast to Group 3, where all animals still had some "pseudo normalization." We noted that the volume of mitral regurgitation indirectly affects the processes of the left atrium remodeling, which is confirmed by an unchanged degree of regurgitation during the study. In our opinion, remodeling occurs from chronic volume overload, and the transition of the preclinical stage to the clinical one occurs without increasing the volume of the regurgitant flow. It was also noted that the fraction of contractility of the left ventricle in animal groups with the progressive remodeling of the left atrium did not change, so we can conclude that contractility does not differ from the norm at the initial clinical stage of endocardiosis. Although the routine use in practice of the attitude of the aorta to the left atrium gives an idea of left ventricular hypertrophy, but since the echocardiographic diagnostic method is partly a subjective method, and when determining this parameter, operators' disagreements may occur during dynamic monitoring, therefore our proposed method for estimating not size, but the cubic volume of the left atrium with further analysis of the dynamic index provides undeniable advantages in the diagnosis of endocardiosis. From the above, it can be concluded that in the group with angiotensin converting enzyme inhibitor therapy and aldosterone antagonist, remodeling processes, the appearance of clinical signs due to endocardiosis of atrioventricular valves, in our opinion, were significantly reduced, as evidenced by the criteria for reducing the appearance of pathological sinus tachycardia of P-mitrale, diastolic dysfunction, an increase in left atrial volumes and a dynamic remodeling index in Groups 1 and 2.

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