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Effects of Pimobendan for Mitral Valve Regurgitation in Dogs

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ABSTRACT. Pimobendan has a dual mechanism of action: it increases myocardial contractility by increasing calcium sensitization to troponin C and it promotes vasodilation by inhibiting PDEIII. This study examined the effects of pimobendan on cardiac function, hemodynamics, and neurohormonal factors in dogs with mild mitral regurgitation (MR). The dogs were given 0.25 mg/kg of pimobendan orally every 12 hr for 4 weeks. With pimobendan, the heart rate and stroke volume did not change, but the systolic blood pressure gradually decreased and the degree of mitral valve regurgitation tended to decrease. Renal blood flow was significantly increased and the glomerular filtration rate was slightly increased at 2 and 4 weeks. Furthermore, over the 4-week period, the plasma norepinephrine concentration decreased significantly, the systolic index increased slightly, the left atrial diameter and the left ventricular diameters decreased significantly, and the heart size improved. Given these results, pimobendan appears to be useful for treating MR in dogs. However, further long-term studies of pimobendan involving a larger number of dogs with mild and moderate MR are needed to establish the safety of pimobendan and document improvements in quality of life.

KEY WORDS: canine, mitral regurgitation, pimobendan.

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Pimobendan has a dual action: it increases myocardial contractility and causes vasodilation. Its positive inotropic effects occur as a result of an increase in calcium sensitization to troponin C without an increase of intracellular calcium ions by phosphodiesterase (PDE) inhibition and without an increase in the energy requirement such as occurs with positive inotropic agents (for example, digoxin and catecholamines) [7, 17]. The vasodilating action of pimobendan in the veins and arteries is due to PDE inhibition. As a result, pimobendan elevates cardiac output, reduces both preload and afterload, and increases myocardial contractility, which causes myofibrosis and remodeling in the failing heart without increasing either myocardial energy or oxygen consumption. Furthermore, pimobendan has some favorable additional properties, such as antithrombotic activity, repression of sympathetic nerve activity, improvement of left ventricular (LV) relaxation, depression of nitrogen oxide (NO) production, as anti-cytokine effects that reduce tumor necrosis factor-α [16, 18].

In human medicine, pimobendan has been reported to be safe and beneficial in patients with congestive heart failure [12, 22]. However, in a long-term study, early clinical trial data demonstrated a trend towards increased mortality in patients with chronic moderate heart failure treated with pimobendan [15]. Nevertheless, a recent study found a reduction in the incidence of adverse cardiac events, including worsening of heart failure and decreased functional capacity, without a significant effect on mortality in patients with mild to moderate congestive heart failure [22].

In veterinary studies, pimobendan has been shown to have favorable effects in dogs with dilated cardiomyopathy (DCM) [8]. There have been several reports dealing with dogs having mitral valve disease (MVD), although the effects of pimobendan on such animals remain controversial. Smith *et al*. reported that dogs with canine heart failure (NYHA Class II-III) caused by myxomatous mitral valve disease that were treated with pimobendan had greater exercise tolerance and a better heart failure outcomes than dogs treated with ramipril [21]. On the other hand, long-term pimobendan monotherapy has been reported to increase the heart murmurs and the mitral regurgitant jet areas in dogs with asymptomatic MVD [3]. Therefore, it is unclear whether pimobendan exerts beneficial effects in dogs with asymptomatic MVD.

The present study examined the effects of pimobendan on cardiac function, hemodynamics, and neurohormonal factors in dogs with asymptomatic mitral regurgitation (MR).

MATERIALS AND METHODS

Four male beagles (body weight, 10.18 ± 1.07 kg) were the subjects of this study. Mild MR was induced in the dogs more than 5 years previously by cutting a part of the mitral valvular chordae tendineae using a flexible alligator forceps.Cutting a part of the mitral valvular chordae tendinieae using a flexible alligator forceps induced mild MR in dogs more than 5 years ago. At the start of the study, each dog had was asymptomatic with cardiomegaly without radiographic signs of pulmonary edema and, a grade IV/VI systolic heart murmur, and was asymptomatic. All the dogs were cared for in accordance with the principles outlined in the Guidebook for the Care and Use of Laboratory Animals approved by the College of Bioresource Sciences, Nihon University.

The dogs were given 0.25 mg/kg pimobendan (Acardi capsules 2.5, Boehringer Ingelheim, GmbHCo., Ingelheim,

Germany) 0.25 mg/kg orally every 12 hr for 4 weeks.

Clinical signs, blood pressure, thoracic x-rays, and 2-dimensional M-mode and Doppler echocardiography, as well as blood biochemistry, were examined before drug administrating and after 1, 2, and 4 weeks after drug administration. All examinations were performed without sedation or anesthesia.

Arterial blood pressure was measured by the oscillometric method. The double product (DP), as an index of cardiac oxygen consumption, was calculated according to the following formula: DP=systolic pressure × heart rate. Vertebral heart size (VHS), as an index of heart size, was measured on lateral thoracic x-rays.

Conventional echocardiography and Doppler measurements were performed on the conscious dogs by the same observer with using an ultrasound unit (Nemio SSA-550A, Toshiba Medical Systems, Tokyo, Japan). The LV end-diastolic diameter (LVEdD), LV end-systolic diameter (LVEsD), LV free wall (LVFW) thickness, and the intraventricular septum (IVS) thickness in diastole and systole were measured on a short-axis M-mode projection of the heart in a plane just below the mitral valve. The aortic (AO) diameter, the left atrial (LA) diameter, and the LA/AO ratio were measured on the short-axis view. Stroke volume (SV), cardiac output (CO), and LV end-diastolic volumes (LVEdV), and LV end-systolic volumes (LVEsD) were measured using the modified Simpson method. As contractile indices, the fractional shortening (FS) and the ejection fraction (EF) were estimated on the right side long-axis parasternal 4-chamber view. The LV outflow and mitral inflow velocities were determined by pulsed Doppler echocardiography. Peak E and A velocities and their ratio (E/A) were determined from mitral inflow recordings of the left apical 4-chamber view.

The velocity of mitral regurgitation was confirmed by continuous-wave Doppler echocardiography; the peak mitral regurgitation velocity (MR Vmax) and the mean rate of LV pressure rise (dP/dt) were determined in the left apical 4-chamber view [1]. The regurgitant stroke volume (RSV) and the effective regurgitant orifice (ERO) were estimated by the proximal isovelocity surface area (PISA) method, which estimates regurgitation volume quantitatively [4, 5, 11].

Renal blood flow (RBF) was measured by an intravenous infusion of sodium para-aminohippurate (PAH) (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan), and the glomerular filtration rate (GFR) was measured by the endogenous creatinine clearance.

Plasma catecholamines, atrial natriuretic peptide (ANP), and aldosterone concentration, and renin activity were analyzed by radioimmunoassay. Blood samples (5 m*l*) were collected from the jugular vein into a tube containing K2-EDTA. The samples were centrifuged for 20 min at 4°C and 1500 × rpm; the plasma was separated and stored at –80°C until analyzed.

Statistical analysis: The results are expressed as means ± standard deviation (SD). Differences in the mean values before and after treatment were analyzed using the paired *t*-test.

RESULTS

Table 1 shows the cardiovascular and hemodynamic changes that occurred with pimobendan administration.

Heart rate did not change, but the systolic blood pressure declined gradually at 2 and 4 weeks ($p<0.05$) and the mean blood pressure decreased at 4 weeks ($p<0.05$). FS and EF increased significantly from baseline at 4 weeks (baseline vs., 4 weeks: 36.8 ± 4.28 vs 40.45 ± 5.26 for FS and 66.65 ± 6.10 vs 71.45 ± 6.58 for EF, $p<0.05$) as did the EF (baseline, $p<0.05$).

DP decreased significantly from baseline (100%) at 1 week (69.15%) and at 4 weeks (74.47%) ($p<0.05$).

LVEdD and, LVEsD, LVEdV, and LVEsV decreased significantly at 2 and 4 weeks, whereas LVFW increased ($p<0.05$). The LA/AO ratio decreased significantly ($p<0.05$).

Although the stroke volume at 4 weeks did not differ from baseline, RSV tended to decrease ($p<0.05$).

Renal blood flow (RBF) increased significantly at 2 and 4 weeks ($p<0.05$); however, there was only a slight increase in GFR (Fig.1).

The plasma norepinephrine concentration decreased significantly, whereas there were no significant differences in the ANP concentration, aldosterone concentration, and renin activity (Table 2).

DISCUSSION

Currently, angiotensin-converting enzyme inhibitors (ACEi) are the treatment of choice for MR in dogs [2, 10]. ACEis reduce the circulating blood volume and lowers blood pressure by actions such as vasodilation and reducing reduction of the release of aldosterone and antidiuretic hormone. Moreover, ACEis have been found to improve and/or delay the remodeling hypertrophy and fibrosis of cardiac myocytes and improve renal function [2, 10].

In both short- and long-term treatment, pimobendan has been shown to have equal or superior clinical effects to ACEi for moderate to severe heart failure caused by DCM or MR [12, 14, 21]. However, Cheboul [3] found that long-term pimobendan treatment was worse than benazepril for treatment of dogs with mild MR with respect to increasing heart murmur grade, FS, and mitral regurgitant jet area; these results were first observed 15 days after treatment and gradually increased over 206 days. In our study, however, RSV was reduced 2 and 4 weeks after treatment. The reduction of RSV is thought to be associated with an increase in forward cardiac output due to a decrease in the afterload (blood pressure) and an increase in systolic function (FS and dP/dt). In addition, the RSV decrease might cause the decline in LVEdD and LVEdV 2 and 4 weeks after the treatment.

In our study, although a slight increase in FS was

Table 1. Cardiovascular and hemodynamic changes after pimobendan administration

			Baseline	1 week	2 weeks	4 weeks
Heart Rate		(beats/min)	109.75 ± 21.58	81.00 ± 7.75	112.50 ± 24.62	92 ± 18.76
Blood Pressure	Systole	(mmHg)	151.90 ± 9.91	142.25 ± 1.45*	139.35 ± 15.35	133.55 ± 6.83*
	Mean	(mmHg)	124.95 ± 8.46	113.25 ± 2.94	115.75 ± 15.08	106.35 ± 10.00*
	Diastole	(mmHg)	103.25 ± 4.46	93.05 ± 4.65	99.35 ± 14.23	88.05 ± 11.57
DP		($\times 10^3$)	16.60 ± 3.05	11.49 ± 1.19*	15.49 ± 2.57	12.36 ± 3.01*
SV		(m*l*)	32.24 ± 9.04	31.58 ± 3.85	27.99 ± 11.23	32.48 ± 10.06
CO		(*l*/min)	2.75 ± 0.68	3.00 ± 0.83	4.26 ± 3.31	3.49 ± 1.10
EF		(%)	66.65 ± 6.10	66.05 ± 7.45	59.8 ± 3.23	71.45 ± 6.58*
FS		(%)	36.80 ± 4.28	36.35 ± 6.04	31.65 ± 2.44	40.45 ± 5.26*
LV E		(cm/s)	92.29 ± 9.64	78.845 ± 7.97	74.015 ± 5.19*	75.54 ± 5.08
LV A		(cm/s)	69.63 ± 6.54	57.84 ± 4.70*	56.00 ± 7.29	51.53 ± 8.51
E/A		(%)	1.33 ± 0.06	1.39 ± 0.05	1.34 ± 0.13	1.52 ± 0.26
Dct		(ms)	88.60 ± 17.20	92.80 ± 10.69	88.30 ± 7.97	80.7 ± 6.82
Peak dP/dt		(mmHg/s)	1654.85 ± 236.17	2330.3 ± 629.95	2517.95 ± 395.23*	2577.50 ± 1157.58
MR Vmax		(cm/s)	575.88 ± 27.56	566.07 ± 42.57	567.64 ± 66.34	537.975 ± 27.29
RSV		(m*l*)	23.70 ± 2.54	24.40 ± 10.94	18.08 ± 1.42*	16.23 ± 5.43*
LVEdD		(mm)	43.39 ± 5.40	40.75 ± 4.18	39.91 ± 5.89*	39.78 ± 4.50*
LVEsD		(mm)	27.40 ± 5.02	25.84 ± 4.07	27.25 ± 3.72	23.77 ± 3.95*
LVFWd		(mm)	7.27 ± 0.94	8.29 ± 1.16	8.12 ± 0.82	8.37 ± 0.59*
LVFWs		(mm)	13.39 ± 1.46	13.48 ± 2.66	12.84 ± 0.62	15.16 ± 1.90*
IVSd		(mm)	8.64 ± 0.89	7.83 ± 1.62	7.69 ± 1.04	8.46 ± 0.47
IVSs		(mm)	10.89 ± 1.32	10.93 ± 1.56	9.94 ± 1.75	11.54 ± 0.95
LVEdV		(m*l*)	50.12 ± 11.05	43.64 ± 1.15	40.93 ± 15.06*	45.47 ± 12.39*
LVEsV		(m*l*)	17.67 ± 2.89	12.08 ± 3.35	12.93 ± 4.14	13.01 ± 3.18*
LA/AO ratio		(%)	1.58 ± 0.14	1.39 ± 0.15*	1.40 ± 0.14	1.30 ± 0.05*
ERO		(cm^2)	0.20 ± 0.01	0.22 ± 0.10	0.19 ± 0.02	0.16 ± 0.05

Data are means ± SD. *: Significant difference from the baseline value ($p<0.05$). SV, stroke volume; CO, cardiac output; EF, ejection fraction; FS, fractional shortening; LV E, left ventricular early velocity; LV A, left ventricular atrium systolic velocity; Dct, decreasing time of mitral regurgitation; peak dP/dt, peak rate of left ventricular pressure; MR Vmax; mitral regurgitant flow peak velocity; RSV, regurgitant stroke volume; LVEdD, left ventricular end-diastolic diameter; LVEsD, left ventricular end-systolic diameter; LVFWd, left ventricular free wall diastolic; LVFWs, left ventricular free wall systolic; IVSd, intraventricular septum diastolic; IVSs, intraventricular septum systolic; LVEdV, left ventricular end-diastolic volume; LVEsV, left ventricular end-systolic volume; LA, left atrial; AO, aorta; ERO, effective regurgitant orifice.

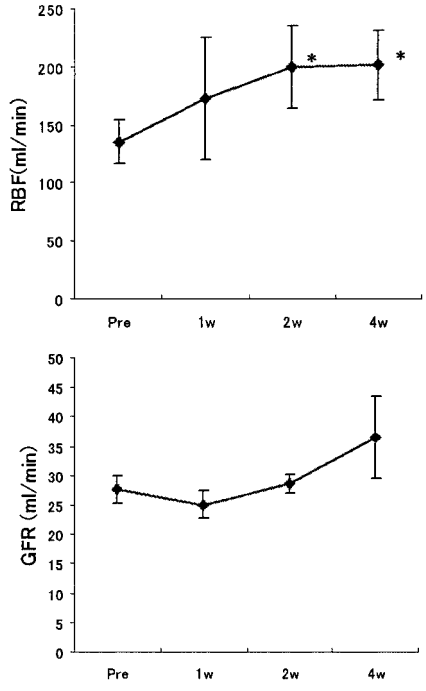

Fig. 1. Glomerular filtration rate (GFR) and renal blood flow (RBF). Data are means ± SD *: Significantly different from the baseline value ($p<0.05$).

observed, blood pressure fell, the left atrial and ventricular volumes were reduced, MR V-max decreased, EF increased, and renal blood flow increased from beginning 2 or 4 weeks after pimobendan administration. However, the serum renin activity and aldosterone concentration remained unchanged. Except for the FS increase, these findings are almost the same as those found for enalapril treatment of mild MR in dogs [2, 10]. In mild to moderate canine MR, the increase in cardiac contractility has generally been thought to be a compensatory mechanism that occurs at the same time that the sympathetic nervous system is activated and vasoconstriction occurs [20]. In our study, the plasma NE level declined along with the improvement in the circulation, and cardiac oxygen consumption decreased after administration of pimobendan. The drop in plasma NE level may have resulted from several factors, such as vasodilation caused by PDE III inhibition [6, 9, 19, 24] and reduction in catecholamine released from the adrenal medulla due to the selective blockade of nicotinic acetylcholine by pimobendan [23]. Therefore, the increase in cardiac contractility by pimobendan might not be caused by sympathetic nerve action, but

Table 2. Changes in circulating neurohormones after pimobendan administration

		Baseline	1 week	2 weeks	4 weeks
Aldosterone	(*n*g/d*l*)	2.33 ± 1.70	2.77 ± 2.11	4.17 ± 2.50	3.57 ± 3.25
Renin activity	(*n*g/dl/h)	1.35 ± 0.25	1.7 ± 0.60	0.84 ± 0.37	1.04 ± 0.48
ANP	(*p*g/m*l*)	18.30 ± 17.46	14.80 ± 9.11	24.13 ± 24.47	20.90 ± 13.27
Epinephrine	(*p*g/m*l*)	260.33 ± 77.73	205.33 ± 54.05	249.00 ± 119.81	212.67 ± 109.51
Norepinephrine	(*p*g/m*l*)	821.33 ± 206.59	443 ± 111.77	473.33 ± 70.04	379.67 ± 137.17*
Dopamine	(*p*g/m*l*)	115.67 ± 63.90	54.33 ± 20.03	57.67 ± 21.39	61.00 ± 33.87

Data are means ± SD. *: Significant difference from the baseline value ($p<0.05$).

rather might be caused by an increased calcium sensitization to troponin C, which strengthens contractility without increasing myocardial energy and oxygen consumption [7]. An increase in cardiac contractility by pimobendan administration is not therefore thought to cause development of myocardial fibrosis and remodeling.

In our study, FS was only shown to significantly increase only 4 weeks after pimobendan therapy. The reason for the insignificant increase in FS 1 and 2 weeks after the treatment is unclear. However, dP/dt was shown to significantly increase even 2 weeks after the treatment. The sensitivity of FS in relation to cardiac contractility is thought to be inferior to that of dP/dt. In addition, the small sample population might have had an influenced in terms of the insignificant increase in FS.

In conclusion, this study demonstrated that pimobendan increases cardiac contractility, causes vasodilation, and reduces the volumetric load of the LV and LA in dogs with asymptomatic MR. Therefore, pimobendan therapy would appear to be as useful as ACEi therapy in dogs with MR. However, further studies are needed to confirm the safety of long-term pimobendan treatment for MR in dogs, as pimobendan has many complex pharmacological actions.

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