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First clinical experience of the use of intravenous pimobendan in acute heart failure in dogs

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Pimobendan, an inhibitor of phosphodiesterase III, is an inotropic, vasodilating drug that has a sensitising effect on calcium channels. It is usually prescribed for the treatment of chronic heart failure. The objective of this study was to determine the effects of using a new injectable formulation of pimobendan in the treatment of hyperacute and severe congestive heart failure in dogs.
This is a descriptive clinical study performed in three dogs with heart disease assessed during acute congestive heart failure and after diuretic therapy in combination with intravenous pimobendan.
The use of intravenous pimobendan in association with diuretic therapy in the acute phase of congestive heart failure resulted in improvements of haemodynamic parameters and clinical signs in the three patients included in the study.

Keywords - hyperacute and acute cardiac heart failure, injectable pimobendan, dog.

INTRODUCTION

Heart failure is a complex clinical syndrome that has been defined as the inability to deliver sufficient blood to meet tissue requirements or the ability to meet these requirements only at high ventricular filling pressures.[1] The haemodynamic changes responsible for the clinical picture of congestive heart failure are, in most cases, the consequences of chronic volume overload of the left ventricle (chronic mitral regurgitation, patent ductus arteriosus) or systolic dysfunction (dilated cardiomyopathy), but can also be caused by acute volume overload due to acute valvular incompetence, for example in the case of rupture of the mitral chordae tendineae or severe valvular endocarditis. The alterations in ventricular load and the intrinsic contractile capacity of the myocardium cause changes in the pressure/volume curve and reduce the cardiac output (Frank-Starling's law). For example, in cases of mitral regurgitation, the valvular incompetence causes the lack of a "real" isovolumetric contraction phase, a reduction of the afterload and a consequent decrease in end-systolic volume. During diastolic ventricular refilling the increased atrial pressure is transmitted to the left ventricle, thereby increasing the volume and pressure of the end-diastolic filling. All this would lead to an increase in the afterload if it were not for the contemporaneous reduction of resistance to outflow due to the mitral regurgitation, which reduces the afterload

The study describes three clinical cases in which injectable pimobendan was used in dogs with acute and hyperacute heart failure.

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during ejection. The result is an increase in the width of the pressure/volume curve, but effective forward flow into the aorta is decreased because some of the blood returns into the left atrium increasing its volume and causing pulmonary venous congestion.
In compensated dilated cardiomyopathy the end-diastolic volume is increased but, within certain limits, the ventricle manages to compensate and maintain a normal stroke volume. In uncompensated heart failure the Frank-Starling mechanism is ineffective and the increased end-diastolic volume and wall stress (Laplace's law) cause venous stasis in the lungs and, therefore, a clinical picture of congestive heart failure, the severity of which depends on the extent of the haemodynamic changes induced by the systolic dysfunction. The administration of pimobendan to Doberman Pinschers prior to their development of clinical signs of dilated cardiomyopathy was found to be effective in prolonging the preclinical period and extending survival.[2]

Acute and hyperacute heart failure are life-threatening clinical conditions and must be treated quickly.

The complex mechanisms involved and the consequences on other organs, primarily the kidneys, lead to the activation of various neurohumoral regulatory processes. Drug treatment must be aimed at counteracting the compensatory mechanisms, which are useful in the short-term but harmful in the long-term.[3] In particular, treatment must reduce the volume overload of the heart chambers (diuretics), control the neurohumoral mechanisms that are activated (ACE-inhibitors), reduce peripheral vasoconstriction (vasodilators) and support cardiac contractility (positive inotropes).[4,5]
Various studies in humans have shown that a single dose of pimobendan administered to patients with acute heart failure can improve right and left ventricular function, thanks to its positive inotropic and lusitropic actions.[6] In veterinary medicine numerous studies have been conducted on the use of pimobendan in the treatment of heart failure in the dog[7,8] as well as in a very variegated range of species including the cat,[9] parrot,[10] pinguin,[11] horse[12] and hedgehog.[13]
In this study we present our experience with the use of a new, intravenous (i.v.) formulation of pimobendan in the treatment of acute heart failure in three dogs with cardiomyopathy.

MATERIALS AND METHODS

This is a descriptive, clinical study carried out at the "Gran Sasso" Veterinary Clinic in Milan. Three dogs were included. Each patient underwent a thorough general and specific clinical examination. Given the animals' respiratory distress, a single X-ray in right lateral decubitus was performed to identify the cause of the dyspnoea. When pulmonary oedema was present, the dog was given a bolus injection of furosemide (2 mg/kg i.v.) together with oxygen therapy. Echocardiographic studies were performed after stabilisation of the patient (respiratory rate < 30 breaths/minute). The patient was then administered pimobendan in a single i.v. bolus injection (0.15 mg/kg) and a continuous infusion of furosemide (1 mg/kg/h). About 6 hours after the bolus injection of pimobendan, the X-ray and echocardiographic studies were repeated. The dogs were kept overnight in hospital, except for one patient with patent ductus arteriosus which underwent percutaneous occlusion of the ductus on the day following the medical therapy. Clinical and instrumental examinations were used to re-evaluate all the patients 1 week later.

The dogs in this study were treated during the acute phase of heart failure with a combination of furosemide and pimobendan, both given intravenously.

CASE REPORTS

Case 1

A male, 13-year old Cocker weighing 15 kg, brought for investigation of dyspnoea and cough which had started the day before. On clinical examination the dog had a respiratory rate of 80 breaths/minute and a heart rate of 120 beats per minute (bpm); the visible mucosal membranes appeared congested, the capillary refill time was slightly prolonged and the femoral pulse was weak. On auscultation of the heart there was a 3/6 holosystolic murmur which was loudest at the apex. Auscultation of the lungs revealed consonant, fine rales. Chest X-ray (Figure 1) showed cardiomegaly, pulmonary venous congestion, increased radio-opacity around the hilum, and an alveolar pattern in the caudal lobes. Echocardiography revealed pronounced increases in both left ventricular end-diastolic volume index (EDVI: 171) and end-systolic volume index (ESVI: 120) as well as an increased left atrium-aorta ratio (LA/Ao: 2.8), marked left ventricular hypokinesia (Figure 2), increased E-point to septal separation (EPSS), central jet mitral regurgitation and mild tricuspid regurgitation. The echocardiographic findings were compatible with dilated cardiomyopathy.
Administration of the previously described treatment led to a progressive slowing in respiratory rate and heart rate, together with an improvement in the patient's clinical condition.

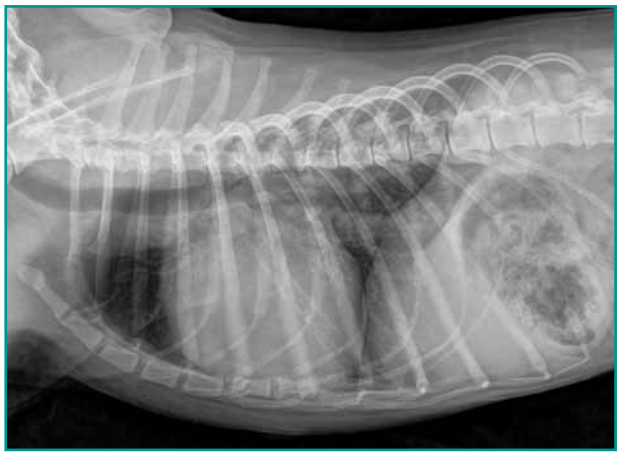

Figure 1 - Latero-lateral X-ray. Note the cardiomegaly, increased sternal contact, enlargement of the area corresponding to the left atrium, pulmonary venous congestion, increased peri-hilar shadowing and the presence of a broncho-alveolar pattern in the caudal lobes.

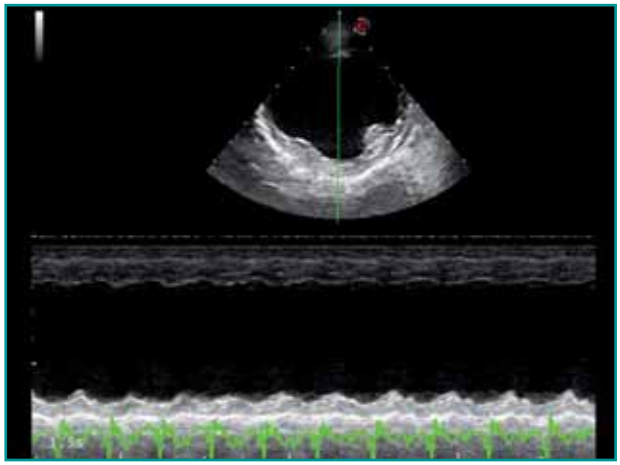

Figure 2 - M-mode echocardiogram of the left ventricle showing an enlarged left ventricle and hypokinesia of the ventricular wall and interventricular septum.

An echocardiographic examination performed 6 hours after the administration of intravenous pimobendan documented the improvement in cardiac parameters (EDVI: 149; ESVI: 99.3; LA/Ao: 2.7). A repeated chest X-ray (Figure 3) showed attenuation of the alveolar pattern and normalisation of the size of the pulmonary vessels. The dog was subsequently discharged with cardiovascular treatment to continue at home (furosemide 2 mg/kg/12 h, ACE-inhibitor 0.5 mg/kg/12 h, pimobendan 0.25 mg/kg/12 h) and a cardiological control was arranged for the following week.

At the follow-up control, the owners reported that the dog's quality of life had improved. On clinical examination the animal's respiratory rate was 40 breaths/minute and his heart rate was 130 bpm, the heart sounds remained the same, whereas the breath sounds were attenuated. Chest X-rays showed moderate, wide-

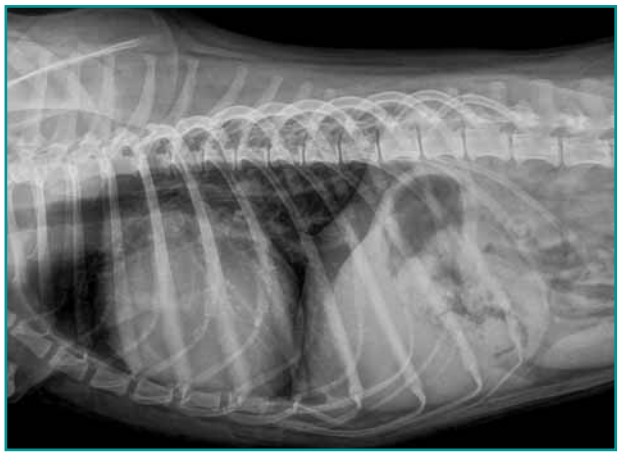

Figure 3 - Latero-lateral X-ray (after diuretic treatment combined with intravenous pimobendan) showing reduced radio-opacity of the lung fields and disappearance of the diffuse alveolar infiltrate.

spread shadowing in the lung fields and normal pulmonary vessels; the dimensions of the cardiac outline were similar to those in the previous images. Echocardiography showed small increases in volumes compared to those recorded during the examination following the administration of intravenous pimobendan (EDVI: 168; ESVI: 109; LA/Ao: 2.4).

A Cocker with pulmonary oedema due to dilated cardiomyopathy was treated with intravenous furosemide and pimobendan until clinically stable.

Case 2

A female, 4-month old German Shepherd with a diagnosis of patent ductus arteriosus was brought to the clinic with severe dyspnoea and tachycardia, inability to stand and stupor. The mucosal membranes were pale. Fine to medium crackles could be heard over the lung fields, while auscultation of the heart revealed a continuous 5/6 murmur cranio-dorsally to the aortic and pulmonary valve auscultation areas.

X-ray showed a diffuse alveolar pattern throughout the lungs (Figure 4) with severe generalised cardiomegaly and an increased vertebral heart score of 12.5. In this case it took 8 hours of continuous furosemide infusion and oxygen therapy to stabilise the animal's clinical condition and resolve the dyspnoea. Once the dog's condition had improved sufficiently to allow the animal to be examined in a lateral recumbent position, the first echocardiographic investigation was performed (EDVI: 221; ESVI: 102; LA/Ao: 2.1). The left cardiac chambers were markedly dilated and systolic function

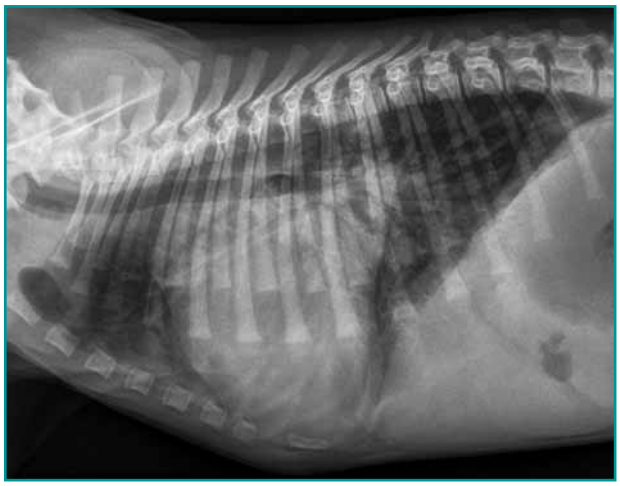

Figure 4 - Latero-lateral X-ray of a female, 4-month old, German Shepherd dog. Note the cardiomegaly, increased size of the region corresponding to the left atrium, pulmonary venous congestion, diffusely increased radio-opacity with a widespread broncho-alveolar infiltrate. Outside the chest, the gastric air bubble seems greatly enlarged.

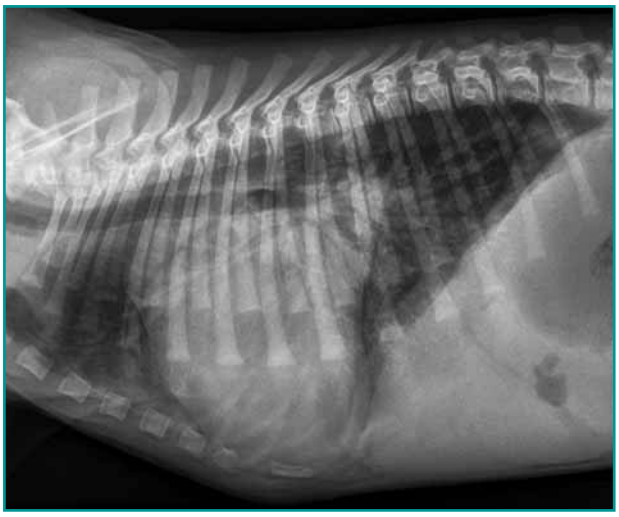

Figure 7 - Latero-lateral X-ray of a female, 4-month old German shepherd dog, performed 6 hours after starting diuretic treatment in combination with intravenous pimobendan. The radiographic signs have improved compared to those in the previous X-rays.

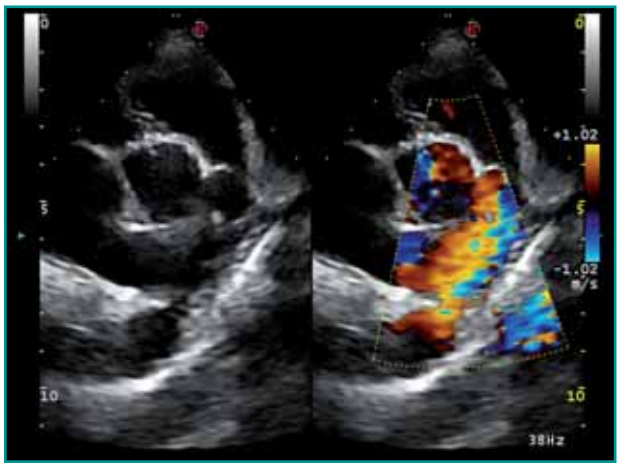

Figure 5 - Left parasternal scan in the cranial short axis, optimised for visualisation of the patent ductus arteriosus. On the right, the colour Doppler confirms the presence of blood flow through the ductus.

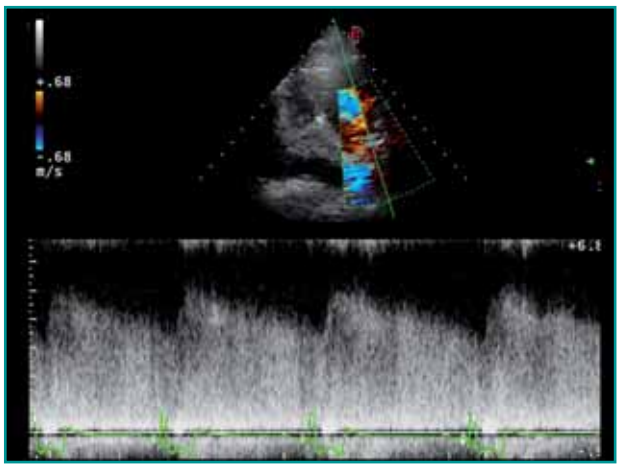

Figure 6 - Left parasternal scan in the short axis allowing correct alignment for the continuous Doppler of blood flow through the patent ductus arteriosus.

was partially compromised. The patency of the ductus arteriosus was demonstrated by the left/right shunt (Figures 5 and 6). Six hours after the start of treatment, improvements in the clinical status and radiographic pictures were observed (Figure 7). The following day the patent ductus arteriosus was closed, percutaneously, with an Amplatz canine ductal occluder (ACDO). After the procedure, an X-ray was taken (Figure 8) and echocardiography revealed decreases in left ventricular end-diastolic and end-systolic volumes (EDVI: 182; ESVI: 101) and hypokinesia due to the drastic reduction in pre-load. The patient was discharged 24 hours later with medical therapy: furosemide 1.5 mg/kg/12 h, ACE–inhibitor 0.25 mg/kg/24 h, and pimobendan 0.25 mg/kg/12 h.

Case 3

The owner of a spayed, 13-year old poodle weighing

A German Shepherd puppy with pulmonary oedema due to a patent ductus arteriosus was treated with furosemide and pimobendan, administered intravenously, until the patient's clinical stabilisation; the patent ductus arteriorus was subsequently closed with an ACDO.

3.5 kg reported that the animal had had dyspnoea and cough for the preceding week and that these signs had worsened in the last 24 hours. The poodle had been receiving treatment with amoxicillin for 5 days. On clinical examination the animal had a respiratory rate of 56

breaths/minute and a heart rate of 144 bpm, the mucosal membranes were pink and the capillary refill time was normal. On cardiac auscultation a holosystolic 4/6 murmur could be heard with the point of maximum intensity over the left apex with irradiation to the right hemithorax. On auscultation of the lung fields, the breaths sounds were increased. Chest X-rays showed increased shadowing in the perihilar area and caudal lobes and an enlarged cardiac outline, particularly in the area corresponding to the left atrium (Figure 9).
Echocardiography revealed marked thickening of the mitral valve flaps prolapsing into the left atrium with first degree rupture of the mitral chordae tendineae (Figure 10), severe left atrial dilatation (Figure 11), pulmonary venous congestion, increased end-diastolic and end-systolic volumes (EDVI: 146; ESVI: 92), ventricular hyperkinesia and mitral regurgitation (Figure 12) and tricuspid regurgitation. The diagnosis of severe mitral regurgitation was made. Rupture of the chordae tendineae of the mitral valve had caused a sudden increase in atrial pressure with acute pulmonary oedema. After 6 hours of treatment with furosemide and i.v. pimobendan, another echocardiographic examination was performed which showed a reduction in ventricular volumes (EDVI: 120; ESVI: 74) and improved systolic function. The last control X-ray showed that the pulmonary oedema had resolved (Figure 13). The following day the patient was discharged with domicilary treatment consisting of furosemide 2 mg/kg/12 h, an ACE-inhibitor 0.25 mg/kg/12 h, and pimobendan 0.3 mg/kg/12 h. The left heart chamber volumes on follow-up, 1 week later, were: EDVI 129; ESVI 80.

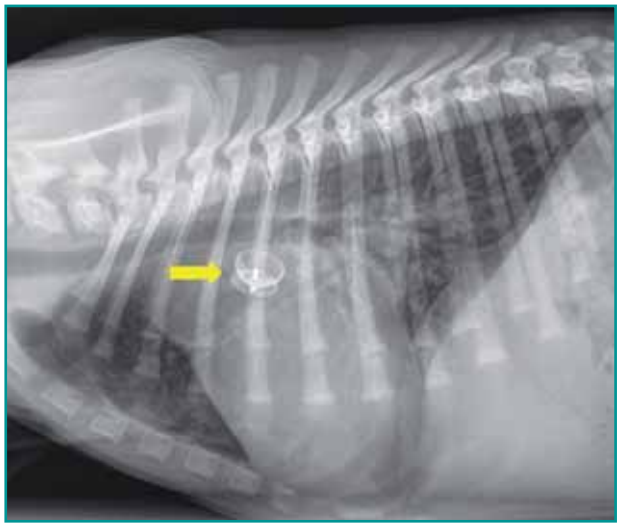

Figure 8 - Latero-lateral X-ray performed after closure of the patent ductus arteriosus by in situ release of an ACDO device (yellow arrow).

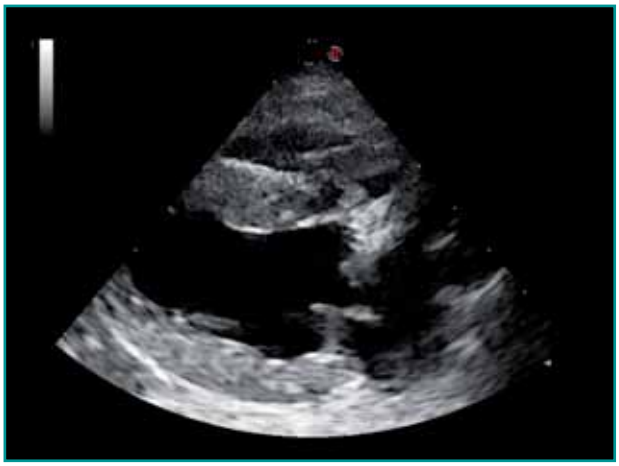

Figure 10 - Right parasternal, long axis (S1) scan showing the mitral valve flap fluttering in the left atrium following primary rupture of the mitral chordae tendineae in a patient with severe, myxomatous mitral valve disease. The left atrium appears greatly enlarged.

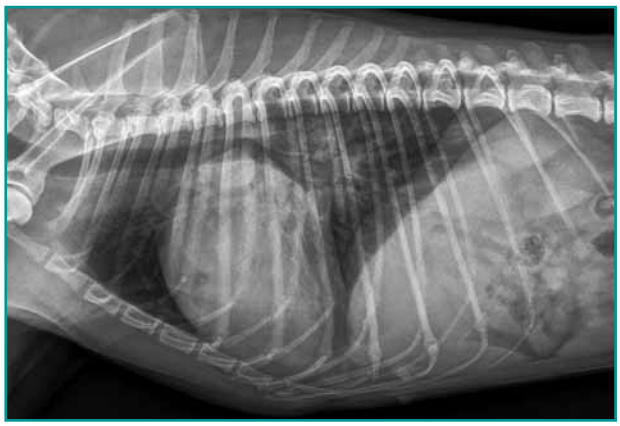

Figure 9 - Latero-lateral X-ray of a spayed, 13-year old poodle. The cardiac outline is enlarged, particular in the area corresponding to the left atrium, with dorsal displacement of the trachea. There is increased radio-opacity in the perihilar area and caudal lobes.

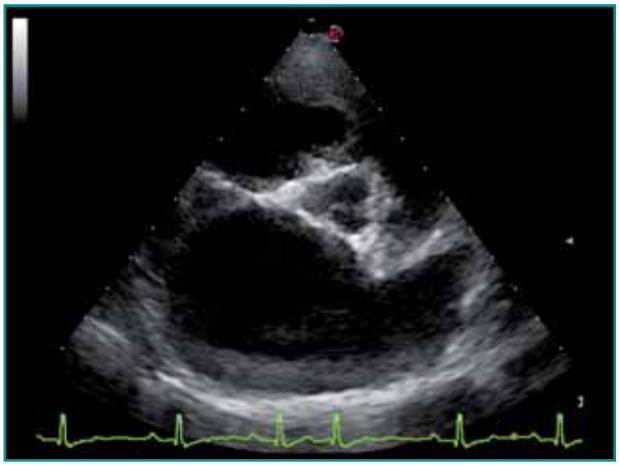

Figure 11 - Right parasternal short axis view of the left atrium/aorta in which the left atrium is clearly greatly enlarged.

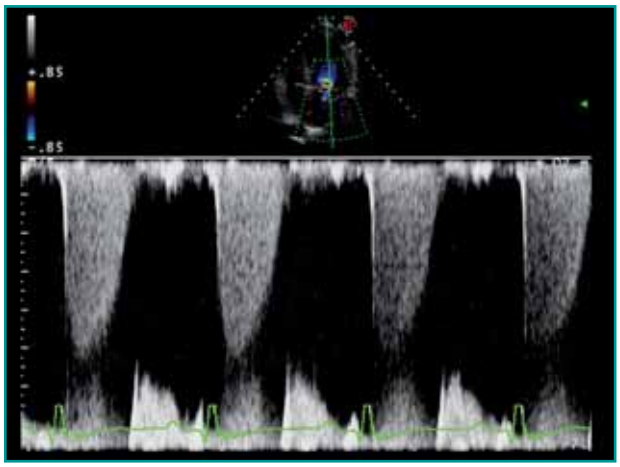

Figure 12 - Continuous Doppler showing mitral regurgitation.

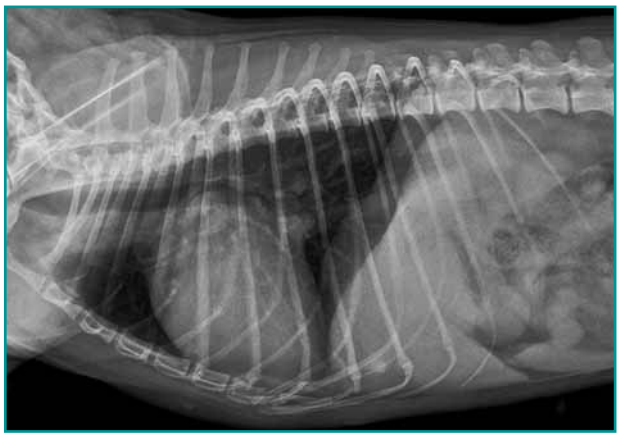

Figure 13 - Latero-lateral X-ray of a spayed, 13-year old poodle, performed 6 hours after the start of diuretic treatment in combination with intravenous pimobendan. There is an improvement in the overall radiographic findings compared to those of the previous X-ray.

DISCUSSION AND CONCLUSIONS

The cases reported here represent a selection of the heart diseases most commonly responsible for acute and hyperacute heart failure in daily clinical practice. Acute pulmonary oedema is a manifestation of acute heart failure and is secondary to a sudden increase in pulmonary venous pressure. The fast increase of left ventricular filling pressure leads to a rapid extravasation of fluid from the pulmonary capillary bed into the interstitial and alveolar spaces. As already mentioned above, the fundamental aim of treatment is to improve the haemodynamic parameters since these are responsible for the clinical manifestations and evolution of the disease. The treatment of congestive heart failure involves the administration of a cocktail of drugs, whose doses should be adjusted appropriately on the basis of the findings of instrumental monitoring (chest X-rays and echocardiography). The data reported in the international literature are concordant regarding the need to use loop diuretics as a life-saving treatment. The combination of such diuretics with pimobendan significantly improves the quality of life of dogs with heart failure. Important clinical studies (VETSCOPE, QUEST)[10,11] demonstrated decreased clinical symptoms and improved quality of life in patients with chronic mitral regurgitation treated with diuretics and pimobendan compared to patients treated with diuretics and an ACE-inhibitor. Furthermore, the survival times of the group treated with pimobendan were significantly longer than those of the other group.[14,15]

Elderly poodle with pulmonary oedema due to ruptured mitral chordae tendineae during severe myxomatous mitral valve disease treated with intravenous furosemide and pimobendan until clinical stabilisation of the patient.

In humans, pimobendan can lower the blood levels of noradrenaline, atrial and brain natriuretic peptides and inflammatory mediators such as endothelin 1, tumour necrosis factor-α, interleukin-1, and interleukin-6, which are released during chronic heart failure.[16-18] In human medicine, the use of drugs belonging to the pimobendan family, in a pre-operative protocol in patients with severe left ventricular dysfunction, was found to be effective in reducing both mortality and the risk of developing low cardiac output syndrome, by optimising cardiac haemodynamic parameters.[19] The improvements in cardiac function are at least partly due to the inotropic, lusitropic and vasodilating effects of pimobendan.[20] The reduction in pre-load and the positive inotropic effect decrease wall stress and shift the pressure/volume curve of the left ventricle towards smaller preload volumes thereby improving forward cardiac output. In the few cases included in this study, the patient's clinical conditions stabilised and their quality of life improved. In conclusion, treatment of acute heart failure in dogs also relies on polytherapy based on furosemide and pimobendan, administered as an i.v. bolus. The main limitations of this study are the small number of patients and the lack of a control group, which prevented statistically significant conclusions from being reached.

The cocktail of drugs commonly used in the treatment of acute congestive heart failure must be adjusted on the basis of the findings of instrumental monitoring (chest X-rays, echocardiography). In the few cases treated here, the combination of furosemide and pimobendan improved clinical symptoms.

KEY POINTS

- Acute and hyperacute heart failure are clinical conditions that must be treated quickly with a combination of drugs.
- This report describes the effects of treatment with intravenous furosemide and pimobendan in three dogs with acute or hyperacute heart failure.
- In the few cases treated, the combination of furosemide and pimobendan improved the clinical picture and findings of instrumental investigations.

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