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Dogs with Eisenmenger Syndrome Can Live a Good and Long Life?

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Mini Review

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ABSTRACT

Eisenmenger syndrome secondary to a ventricular septal defect with right-to-left shunting and erythrocytosis is often secondary to the development of pulmonary hypertension. Long-term treatment should be focused on controlling clinical signs, improving quality of life and prolonging survival of affected dogs. Selective pulmonary vasodilatory drugs are the first-line therapy indicated by the guidelines. In particular, sildenafil citrate is well tolerated, with no reported side effects, even at higher doses and can also help to manage erythrocytosis.

Keywords: Congenital heart disease; Right-to-left shunting; Treatment; Polycythemia; Dog

INTRODUCTION

Treatment of congenital diseases can be a challenge, because available information might be limited. In particular, Ventricular Septal Defect (VSD) in dogs accounts for 4.8% to 12.3%. Bidirectional or pulmonary-to-systemic shunting (reversed shunting) is less frequent, accounting for 3.8% of dogs with VSD [1,2].

The direction of blood flow through the VSD is related to the size of the defect and to vascular resistance of circulation. As the systolic pressure in the left ventricle is almost 120 mmHg in comparison to 20 mmHg in the right ventricle, the flow direction is from left-to-right in most shunt.

In dogs with large VSD, shunt reversal usually occurs before the age of 6 months and develops when the pressure on the right side of the heart increases and approaches the pressure in the left side, mostly secondary to pulmonary hypertension, due to vascular changes.

Indeed, chronically increase in pulmonary blood flow and pressure causes shear and circumferential stresses on the endothelium, causing modification of the vascular walls.

This type of shunt causes mixing of oxygenated and non-oxygenated blood and persistent hypoxemia, determining the production of erythropoietin by the kidney and development of secondary erythrocytosis, hyperviscosity and hypoperfusion. The sum of clinical signs, such as exercise intolerance, exertional dyspnea and syncope are called Eisenmenger Syndrome (ES).

The right ventricular is a low-pressure chamber and hardly tolerates afterload increase, so surgical correction of the defect is generally contraindicated in patients with ES, because VSD allows partial relief of the right ventricular overload. Therefore, lifelong medical therapy should be administered to improve the quality of life and prolong the survival of affected dogs [3].

LITERATURE REVIEW

Long-term medical treatment

In dogs affected by right-to-left shunting and polycythemia, morbidity and mortality are generally thought to be linked to the effects of chronic hypoxemia and erythrocytosis and long-term medical management is focused on controlling these aspects [3,4]. The standard approach to reduce blood viscosity is based on repeated phlebotomy or administration of myelosuppressive drugs (i.e., hydroxyurea), whereas decrease Pulmonary Hypertension (PH) is obtained with selective pulmonary vasodilators such as phosphodiesterase type-5 inhibitors (i.e., sildenafil citrate) or endothelin receptor antagonists (i.e., bosentan) [5,6].

Some concerns are related to chronic treatment with the previously indicated therapies. Periodic phlebotomy may be helpful in relieving symptoms and the recommendation is to maintain the hematocrit between 58%-65%. Symptoms may recur in about a month and the procedure needs to be repeated several times a year. Although frequent phlebotomies can lead to iron deficiency and microcytosis, with exacerbation of the hyperviscosity [3]. In the long-term this approach is expensive and time-consuming for the owner and could lead to low compliance in the treatment.

Hydroxyurea is an antineoplastic agent that causes reversible bone marrow suppression. Some side effects were reported, such as anorexia, vomiting, bone marrow hypoplasia, sloughing of toe nails, alopecia and spermatogenic arrest. The most effective dose regimen for chronic control of polycythemia in dogs is unknown and cytopenia is the primary cause for dosage change or discontinuation of therapy, during treatment of myeloproliferative diseases [7].

Endothelin receptor antagonists reduce vasoconstriction, smooth muscle cell proliferation and fibrosis in the pulmonary vessels, by blocking the endothelin 1 receptor [5]. Phosfodiesterase-5 inhibitors induce vasodilation by inhibiting the degradation of cGMP, a second messenger for nitrate oxide and they are associated with antiproliferative effects on pulmonary vascular smooth muscle cells. Both selective pulmonary vasodilatory drugs alleviate the symptoms of the ES, improving quality of life and prolongs survival, but they are expensive (in particular bosentan) and may reduce systemic pressure, leading to an increase in right-to-left shunt and further decreased SpO2 [4].

In veterinary medicine, there are few studies reporting the treatment of reversed shunting in congenital heart disease in dogs. Three case series and a retrospective multicenter study have described different treatments for reversed Patent Ductus Arteriosus (PDA) in dogs [7-10]. The first study reports long-term management of

erythrocytosis in 3 dogs (8 years, 3 years and 11 months respectively), performing phlebotomy "as needed", depending on clinical findings [7]. In the second study, 4 dogs received hydroxyurea for several months (22, 12, 10 and 6 months respectively) to alleviate clinical signs secondary to erythrocytosis. The authors empirically chose to use intermittent dosing (50 mg/kg PO every 48 h) to induce a gradual reduction of hematocrit and minimize the occurrence of adverse effects [8]. In the third study, the administration of sildenafil citrate (0.5 mg/Kg twice daily) improved clinical signs and erythrocytosis in 5 dogs, over a 3-months period [9]. The retrospective study is more recent than the case series and reported the management of 35 dogs with bidirectional and right-to-left PDA, showing a median survival time of 5 years, when dogs without cardiac failure are considered. Moreover, dogs lived longer when treated with sildenafil citrate at presentation, with a median total dose of 3 mg/kg/d (5 years *vs.* 8 months without sildenafil, p=0.03) [10].

In the 2020, ACVIM consensus statement guidelines for pulmonary hypertension have provided a useful classification and recommend the administration of pulmonary vasodilators for pulmonary arterial hypertension associated with congenital cardiac shunts in dogs (ACVIM classification 1d1). Although, treatment by periodic phlebotomy and hydroxyurea can also suggested, as an alternative treatment, to decrease red cell volume in dogs with clinical signs secondary to reversed shunt and erythrocytosis.

A recently published case report describes the long-term management (9 years) of a dog with ES secondary to large muscular VSD with bidirectional shunting [11]. Early administration of sildenafil citrate, with dose progressively increased up to 2 mg/Kg every 8 h, has allowed the dog a good quality of life with moderate physical activity (running, playing and barking). Hematocrit has also been maintained near 65% by therapy and only occasional phlebotomies have been required, before changing the dose. No adverse effects, such as systemic hypotension, were observed.

Whereas echocardiographic parameters were not available for estimating pulmonary pressure and the shunt direction did not change over the years, therapy was monitored using hematocrit and clinical signs. A hematocrit around 80% has been associated with increase in heart rate (>130 bpm), respiratory rate (>30 breath per minutes), syncopal occurrences and decreased physical activity, with prolonged panting after exercise. Looking at human patients with pulmonary hypertension, the determination of exercise capacity plays an important role in the evaluation of disease and is correlated with survival, functional class, hemodynamics, echocardiographic parameters, biomarkers and health-related quality of life [12].

Lastly, Kim et al. have reported the medical management with sildenafil and oxygen inhalation in two Maltese dogs with reversed shunt, one with PDA and the other with a VSD (perimembranous). The dogs returned to clinically normal conditions after two and one months of therapy, respectively. Echocardiographic findings revealed persistent bidirectional shunt, but left-to-right shunt was more dominant than right-to-left shunt, in both dogs. The Author's hypothesis was that the pulmonary vascular lesions present in these dogs were reversible and not as severe as expected, despite the severe pulmonary hypertension [13]. Furthermore, the dog with the VSD did not have erythrocytosis (hematocrit was 43%), indicating a mild degree of hypoxia or a short-term duration of this condition.

The authors of the previous case reports prescribed home oxygen therapy (oxygen inhalation therapy 5 times/day for 20 min each) in addition to sildenafil citrate. It was demonstrated that chronic hypoxia causes pulmonary vasoconstriction, changes in vascular walls and increased pulmonary vascular resistance. Although in human medicine there is no evidence of survival benefits in patients with pulmonary hypertension treated with long-term

oxygen therapy, its administration may improve tissue oxygenation and prevent complications due to chronic hypoxemia. On the contrary, long-term oxygen therapy is indicated in pulmonary hypertension due to severe chronic obstructive pulmonary disease [14].

According to the guidelines, the first-line treatment of pulmonary hypertension in dogs consists of dose escalation of sildenafil (the most reported phosfodiesterase-5 inhibitor in veterinary literature) that specifically target the vascular nitric oxide pathway.

Administration of sildenafil citrate reduces symptoms (syncope and fatigue), helps control polycythemia and may induce shunt reversal [11,12]. The latter condition may occur when pulmonary hypertension is due to reversible vascular dysfunction, such as resulting from medial hypertrophy and intimal proliferation. As disease progresses, irreversible lesions occur (plexiform lesions and arteritis) [15]. Therefore, in some cases an early and appropriate treatment might reduce the amount of shunt from right-to-left, decreasing the systemic hypoxia and the development of Eisenmenger syndrome [12].

Echocardiographic assessment, such as tricuspid regurgitation velocity and pulmonary arterial pressure, may show no or slight changes, because pulmonary blood flow may increase, as pulmonary vascular resistance decreases [4]. Therefore, clinical and laboratory assessments are particularly important to modulate therapy and periodic follow-ups should be scheduled throughout the dog's life, to evaluate symptoms and hematocrit value. Sensitizing owners about the importance of monitoring some clinical signs such as polypnea, color mucous membrane, syncope episodes and easy fatigue can be essential to promptly detect worsening of ES. Indeed, the identification of these symptoms could indicate an increase in hematocrit that might require a change in therapy, or other health issues causing dehydration and hemoconcentration.

Long-term treatment with sildenafil is well tolerated and few side effects were reported [10-12]. However, ACVIM guidelines indicated that pulmonary artery vasodilators might induce pulmonary non-cardiogenic edema in some dogs in case of “reactive” or “responsive” pulmonary arteries. Then, authors suggested starting with a conservative dosage of sildenafil citrate (0.5 mg/kg PO q8 h).

Two disadvantages could be associated with the sildenafil treatment: Short half-life, ideally necessitating q8 h dosing and cost. In a recent study, tadalafil (2 mg/kg, administered once daily) appeared not inferior to sildenafil and could considered an alternative in dogs with moderate to severe pulmonary hypertension [4].

CONCLUSION

Managing Eisenmenger syndrome secondary to ventricular septal defect in dogs requires a multifaceted approach to ensure a good quality of life and extended survival. Early diagnosis, owner education and individualized medical therapy, including sildenafil citrate are essential. Regular monitoring of clinical signs, hematocrit levels and periodic follow-ups enable timely adjustments in treatment plans. While challenges such as cost and compliance exist, advancements in pharmacologic therapies, including alternatives like tadalafil, provide promising outcomes. Veterinarians should emphasize the importance of collaboration with pet owners to optimize care, addressing hypoxemia, erythrocytosis and pulmonary hypertension effectively to achieve long-term stability and wellness for affected dogs. Hence, a veterinarian who diagnoses VSD and ES can tell the owners that, with cooperation and medical treatment, dogs can have a long and good life.

REFERENCES

1. Brambilla PG, et al. Epidemiological study of congenital heart diseases in dogs: Prevalence, popularity, and volatility throughout twenty years of clinical practice. PLoS One. 2020;15:e0230160.
2. Bomassi E, et al. Signalment, clinical features, echocardiographic findings and outcome of dogs and cats with ventricular septal defects: 109 cases (1992-2013). J Am Vet Med Assoc. 2015;24:166-175.
3. Ettinger SJ, et al. Textbook of Veterinary Internal Medicine: Textbook of Veterinary Internal Medicine-eBook. Elsevier Health Sciences. 2016.
4. Reinero C, et al. ACVIM consensus statement guidelines for the diagnosis, classification, treatment and monitoring of pulmonary hypertension in dogs. J Vet Intern Med. 2020;34:549-573.
5. Galiè N, et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blinded, randomized, placebo-controlled study. Circulation. 2006;114:48-54.
6. Chau EM, et al. Effects of chronic sildenafil in patients with Eisenmenger syndrome *versus* idiopathic pulmonary arterial hypertension. Int J Cardiol. 2007;120:301-305.
7. Moore KW, et al. Hydroxyurea for treatment of polycythemia secondary to right-to-left shunting patent ductus arteriosus in 4 dogs. J Vet Intern Med. 2001;15:418-421.
8. Côté E, et al. Long-term clinical management of right-to-left ("reversed") patent ductus arteriosus in 3 dogs. J Vet Intern Med. 2001;15:39-42.
9. Nakamura K, et al. Effects of sildenafil citrate on five dogs with Eisenmenger's syndrome. J Small Anim Pract. 2011;52:595-598.
10. Greet V, et al. Clinical features and outcome of dogs and cats with bidirectional and continuous right-to-left shunting patent ductus arteriosus. J Vet Intern Med. 2021;35:780-788.
11. Bruno B, et al. Eisenmenger syndrome in a dog with ventricular septal defect: Management for more than 9 years. Front Vet Sci. 2024;11:1-8.
12. Demir R, et al. Six-minute walk test in pulmonary arterial hypertension. Anatol J Cardiol. 2015;15: 249–254.
13. Kim Y, et al. Echocardiographic changes in the progress of reverse shunt and improvement to left-to-right shunt after medical treatment in dogs with bidirectional patent ductus arteriosus or ventricular septal defect: A report of two cases. Vet Med Sci. 2023;9:1044-1052.
14. Hardinge M, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax. 2015;70 Suppl 1:i1-i43.
15. Budhiraja R, et al. Endothelial dysfunction in pulmonary hypertension. Circulation. 2004;109:159-165.