NOTE *Internal Medicine*

A Case of Long-Term Sildenafil Therapy in a Young Dog with Pulmonary Hypertension

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ABSTRACT. A 7-month-old male Papillon was presented to us with mild dyspnea, cyanosis and a diastolic murmur detected by cardiac auscultation. Echocardiography revealed severe pulmonary arterial hypertension (PH), and administration of 1 mg/kg of oral sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, twice daily was initiated. Exercise capacity, cyanosis, dyspnea and cardiac murmur were improved after therapy for 4 weeks. PCV was remarkably high (74%) after therapy for 3 years, however, increasing the dose of sildenafil decreased this value (60%). Follow-up after therapy for 4 years revealed that treatment with oral sildenafil only continued to provide the dog with an excellent quality of life, without any side effects.

KEY WORDS: canine, pulmonary hypertension, sildenafil.

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The selective phosphodiesterase type 5 (PDE5) inhibitor sildenafil citrate is a potent pulmonary vasodilator that causes the concentration of cyclic guanosine monophosphate to increase, which subsequently result in nitric oxide-mediated vasodilation [2, 4, 11, 12, 17]. Sildenafil decreases pulmonary artery pressure and pulmonary vascular resistance, and increases cardiac output without decreasing systemic blood pressure or increasing wedge pressure in humans [9]. Additionally, sildenafil might also affect vascular remodeling [2]. Sildenafil has been used to successfully treat pulmonary artery hypertension (PH) in both children and adults [1, 4, 8, 15]. Bach *et al.* have also assessed the efficacy and safety of sildenafil in dogs with PH [2]. Short-term tadarafil, a long-acting oral PDE5 inhibitor, has been used to treat a dog with end-stage PH [14]. The specific selectivity of PDE5 in dogs is unknown, and sildenafil and tadarafil might affect systemic vascular resistance and blood pressure [2, 14]. The median survival time of dogs in a study by Bach *et al.* was 91 days, whereas the survival reported in a retrospective study by Johnson *et al.* was 3 to 3.5 days. Treatment of dogs with PH has rarely been effective historically [2]. We examined the efficacy of long-term sildenafil therapy (for about 4 years) in a young dog with severe PH diagnosed by echocardiography.

A 7-month-old male Papillon weighing 2.3 kg developed mild dyspnea on exertion, cyanosis during excitement, fatigue after exercise and a heart rate of 150 beats per minute. There was no other relevant medical or drug history. Thoracic auscultation revealed a grade I/VI-II/VI diastolic murmur over the pulmonic area with no respiratory abnormalities. An electrocardiogram demonstrated right axis division (mean electrical axis, 159°). Lateral and ventrodorsal thoracic radiography revealed severe cardiomegaly with a substantial increase in sternal contact and an elevated cardiac apex, which are two common signs of right cardiomegaly. Lateral and ventrodorsal thoracic radiography showed no significant tracheal, bronchial or pulmonary lesions. Creatine phosphokinase was slightly increased and was the only blood reference value to exhibit any abnormality. Heartworm antigen was negative and abdominal ultrasound revealed no abnormalities. Two-dimensional (2D) and M-mode echocardiography, color flow imaging and spectral Doppler examinations were performed. The dog was remained conscious under gentle restraint without sedation throughout the ultrasound examination. Echocardiography demonstrated right ventricle (RV), right atrium (RA), and pulmonary artery enlargement (Fig. 1), with paradoxical septal motion, systolic septal flattening and a reduced left ventricular internal diameter. Color flow Doppler echocardiography from the right ventricular outflow tract showed regurgitation from the pulmonic valve to the RV at diastole in a mosaic pattern. Continuous wave Doppler sonography showed that the peak pulmonic regurgitation velocity was 5.1 m/s. The modified Bernoulli equation revealed a 104 mmHg gradient between the PA and RV (Fig. 2), which represents the diastolic pulmonary arterial pressure, with confirmed severe PH (normal range of pulmonary arterial pressure: 10–20 mmHg). There were no intracardiac shunts or pulmonic stenosis. Cardiac catheterization was not performed. We diagnosed the dog with severe pulmonary hypertension (PH) and pulmonic regurgitation and administered 1 mg/kg of oral sildenafil (Viagra, Pfizer) twice daily. Exercise capacity, cyanosis, dyspnea and cardiac murmur were improved after therapy for 4 weeks. After 3 months, pulmonic regurgitation velocity estimated by Doppler echography was 4.9 m/s and diastolic pulmonary arterial pressure was 96 mmHg. After 3 years of therapy, hematological findings revealed severe polycythemia (PCV, 74%), which was improved (60%) by

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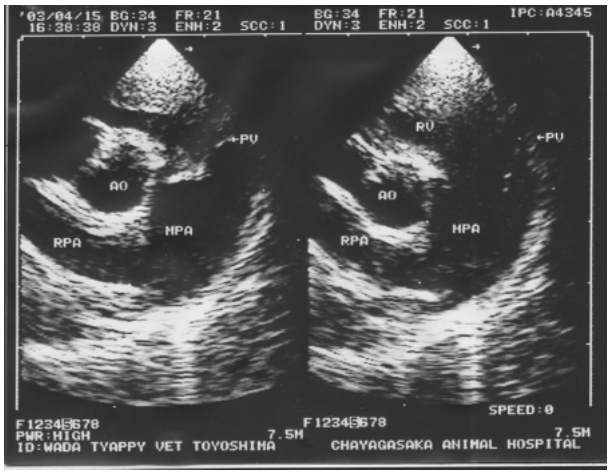

Fig. 1. Two-dimensional (2D) echocardiography at first examination. Right ventricle (RV), right atrium (RA) and pulmonary artery enlargement can be seen from the right parasternal location short-axis view.

increasing the medication frequency from 2 to 3 doses per day (Table 1). Ventrodorsal thoracic radiography during a follow-up visit after therapy for 4 years revealed an intense vascular shadow on the lungs, and cardiac auscultation revealed a slowly worsening diastolic murmur. However, the dog continued to have an excellent quality of life with administration of only oral sildenafil, without any side effects.

Pathologic PH is characterized by abnormally high pressure in the pulmonary arterial circulation with a high endothelin-1 plasma concentration [16] and is conventionally divided into primary and secondary etiologies. It occurs most often secondarily to left-sided heart failure, increased pulmonary blood flow or increased pulmonary vascular resistance by conditions such as obstructive pulmonary vascular disease, hyperviscosity reactive arterial vasoconstriction or pulmonary parenchymal disease. The underlying causes in dogs include right-to-left shunting, pulmonary thromboembolism, chronic pulmonary disease, chronic valvular heart disease, left-sided congestive heart failure and,

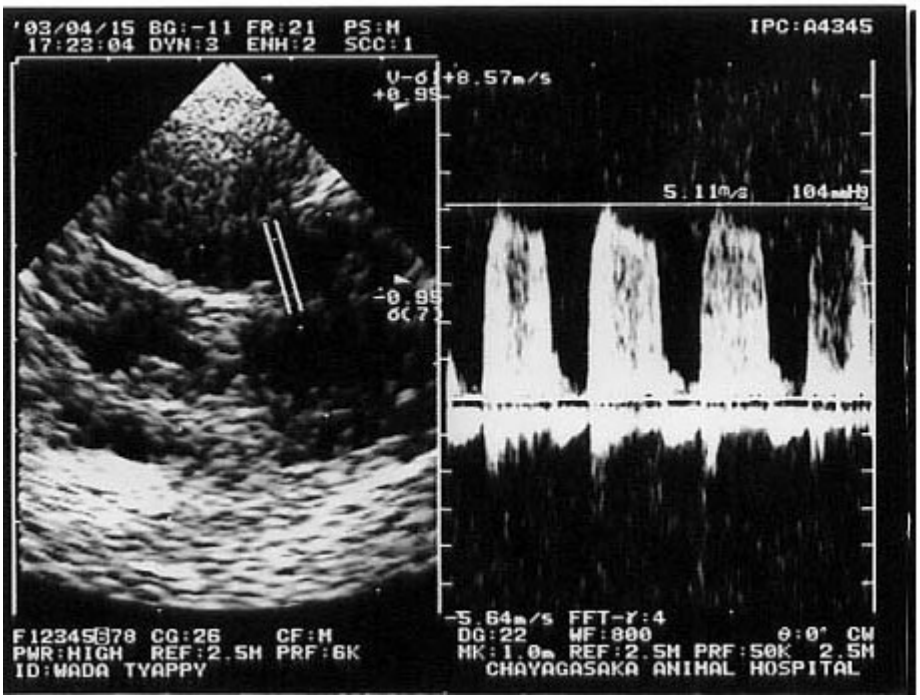

Fig. 2. Continuous wave Doppler echocardiography at the pulmonic valve. The peak pulmonic regurgitation velocity was 5.1 m/s, and the diastolic pulmonry arterial pressure was 104 mmHg. This indicates severe PH.

Table 1. Changes in polycythemia

	First examination	Week[a)]	0	2	4	8	12
PCV (%)	51		74	70	68	61	60
HGB (g/d*l*)	18.4		24.6	23.8	22.2	21.6	20.8
Sildenafil	Twice daily		Three times daily→				

a) PCV was remarkably high after therapy with sildenafil for 3 years. Therefore, the dose was increased.

most commonly, heartworm disease [3, 10, 14]. In one instance, PH was related to *Angiostrongylus vasorum* [10]. Primary PH is rare in dogs and is an aggressive condition characterized by progressive elevation of pulmonary artery pressure with secondary right ventricular failure and death [2, 14]. A diagnosis of primary PH is reached by a process of exclusion. We diagnosed severe PH on the basis of echocardiographic findings. Cardiac catheterization is the definitive diagnostic procedure for PH. It can estimate any reversibility of elevated pulmonary vascular resistance and exclude other conditions. However, dogs are often diagnosed based on information derived from echocardiography [2, 14, 18] because cardiac catheterization is accompanied with aggressive risk. Echocardiography can give a good estimation of pulmonary arterial pressure when the Bernoulli formula is used and congenital heart disease is excluded [2, 6, 7, 13, 14, 18]. Johnson *et al.* studied 53 dogs with Doppler-derived evidence of pulmonary hypertension in which a pulmonic regurgitant velocity of ≥2.2 m/s was considered abnormal and indicative of PH [7]. The initial finding for dogs with PH is vasoconstriction due to vasoreactive medial hypertrophy progressing to intimal fibrosis and plexiform arteriopathy causing fixed obstruction [5]. The human pathological classification also characterizes canine lesions. The therapeutic goal is pulmonary vasodilation while the vessels remain reactive [1], which is related to both age and degree of abnormal vascular resistance derived from vessel constriction or fixed arteriopathic obstruction [5]. Most animals with primary PH present clinical symptoms when they are quite young. Because primary PH is determined by a process of exclusion, the amount of evidence for the current case is arguably insufficient. However, if the dog described herein did indeed have primary PH, then the positive outcome could be explained by the early administration of sildenafil.

The reported adverse effects of sildenafil in humans comprise headache, dyspepsia, dizziness, visual disturbances, nasal congestion, priapism, myalgia, back pain and flushing. Cutaneous flushing in the inguinal region has been reported previously [2], and although other adverse effects might be difficult to recognize, the dog described herein did not develop any known adverse effect.

The disadvantage of sildenafil is its short duration of action, but this can be overcome by administration of 2 or 3 doses daily as in the present case. Despite the severity of PH, the clinical symptoms and survival of the dog described here significantly improved with only administration of oral sildenafil. His exercise capacity was obviously improved, and he continues to have a good quality of life without obvious adverse effects despite prolonged administration of sildenafil. Although his PCV remained quite high, it was improved by increasing the therapeutic dose of sildenafil. Our results indicate that oral sildenafil therapy can play a positive therapeutic role in long-term management of canine PH.

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