Journal of Veterinary Cardiology (2019) **23**, 96—103

Journal of Veterinary Cardiology
ESVC

www.elsevier.com/locate/jvc

Case Report

Effect of sildenafil and pimobendan on intracardiac heartworm infections in four dogs

S.S. Tjostheim, DVM*, H.B. Kellihan, DVM, K.A. Grint, DVM, R.L. Stepien, DVM, MS

Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, 2015 Linden Dr. Madison, WI 53706, USA

Received 27 August 2018; received in revised form 28 January 2019; accepted 18 February 2019

KEYWORDS
Canine;
Dirofilariasis;
Medical management

Abstract Four dogs, referred for management of heartworm (HW) disease, were found to have HWs entangled in their tricuspid valve apparatus. None of the dogs were actively hemolyzing or showed signs of acute cardiovascular collapse that would have necessitated emergency transvenous HW extraction, and surgery was not performed at time of presentation. The dogs received pimobendan and sildenafil within 24 h of identifying HW in the tricuspid valve apparatus, and the HW moved to the pulmonary arteries within 2 days in most cases (median 2 days, range 1—14 days). All dogs survived to discharge from the original hospital admission and were subsequently treated with adulticide (melarsomine) without complication. All dogs were HW antigen negative 6 months after their last melarsomine injection. Four dogs appeared to respond positively to medical management aimed at decreasing pulmonary arterial pressure and improving the right ventricular function, but movement of HW out of the heart for other reasons cannot be excluded. This therapeutic option is not advised when dogs with HW disease are presented for acute collapse, ongoing hemolysis, and hypotension as surgical extraction is still considered the best option in these cases. It remains unknown if medical management is a safe option for all dogs with intracardiac HW without clinical signs of caval syndrome. Controlled prospective studies are required to determine the efficacy and safety of this treatment regimen in comparison with surgical extraction.

* Corresponding author.
E-mail address: sonja.tjostheim@wisc.edu (S.S. Tjostheim).

https://doi.org/10.1016/j.jvc.2019.02.001
1760-2734/

Abbreviations

CS	caval syndrome
HW	heartworm(s)
MPA	main pulmonary artery
PAP	pulmonary arterial pressure
PH	pulmonary hypertension
RA	right atrium
RV	right ventricle
TR	tricuspid regurgitation
TV	tricuspid valve

Case 1

A 3-year-old female spayed mixed breed dog was referred for suspected right-sided congestive heart failure secondary to heartworm (HW) disease. She had been receiving doxycycline (10.5 mg/kg orally every 12 h) and ivermectin (136 mcg orally monthly) since adoption, 4 weeks earlier. She was presented to the referring veterinarian for acute tachypnea and abdominal distention. A new heart murmur was reported.

At presentation, she was tachypneic and her bronchovesicular sounds were increased bilaterally. She had a grade 4/6 right apical systolic heart murmur and a grade 2/6 left apical systolic heart murmur with a severely distended abdomen and a fluid wave on ballottement. Initial blood work showed that she was mildly anemic (packed cell volume [PCV] 30%, reference 40—59%; Table 1). The right ventricle (RV) was moderately enlarged on thoracic radiographs, and there were patchy alveolar pulmonary infiltrates in the right caudodorsal lung fields. The main pulmonary artery (MPA) was severely enlarged, and the pulmonary arterial vasculature was distended and tortuous (Fig. 1A and B). Echocardiography showed HWs in the MPA, RV, tricuspid valve (TV) apparatus, and right atrium (RA) (Fig. 2A). There was evidence of severe pulmonary hypertension (PH), including a tricuspid regurgitation (TR)—estimated pulmonary pressure of 130 mmHg, severe septal flattening, moderate concentric RV hypertrophy, and severe MPA dilation. A brief abdominal ultrasound confirmed free peritoneal fluid. The patient was prescribed sildenafil (1.4 mg/kg orally every 8 h), and she continued to receive dexamethasone (0.14 mg/kg IV every 24 h), doxycycline (5.2 mg/kg orally every 12 h), and furosemide (2.1 mg/kg orally every 12 h). The doxycycline dose was decreased due to concern that it may be a contributing cause of dog's hyporexia while in hospital.

The following day, the dog appeared brighter and her respiratory rate and effort had improved. Her

Table 1 Hematology, biochemistry, and urinalysis results.

Case	Hematological abnormalities	Biochemistry abnormalities	Urinalysis
1	2.5 weeks before presentation: Hematocrit 33% (ref. 36—60) Monocytes 1.1 × 10^3/uL (ref. 0.0—0.8) On admission: PCV 30% (ref. 40—59)	2.5 weeks before presentation: Total protein 8.3 g/dL (ref. 5.0—7.4) Albumin 2.2 g/dL (ref. 2.7—4.4) Globulin 6.1 g/dL (ref. 1.6—3.6) On admission: Total protein 9 g/dL (ref. 5.0—7.5)	Not performed
2	On admission: Hematocrit 34% (ref. 39—57) Platelets 94 × 10^3/uL (ref. 175—500) Leukocytes 17.6 × 10^3/uL (ref. 5.0—14.0) Neutrophils 12.1 × 10^3/uL (ref. 2.6—10.0) Eosinophils 2.3 × 10^3/uL (ref. 0.1—1.7)	On admission: Total protein 7.9 g/dL (ref. 4.8—6.9) Globulin 4.1 g/dL (ref. 2.2—3.5) AST 187 U/L (ref. 21—53)	On admission: USG 1.037 Protein 1+ Bilirubin 3+
3	On admission: Hematocrit 27% (ref. 39—57) Platelets 69 × 10^3/uL (ref. 175—500) Leukocytes 17.7 × 10^3/uL (ref. 5.0—14.0) Neutrophils 14.5 × 10^3/uL (ref. 2.6—10.0) Bands 0.7 × 10^3/uL (ref. 0.0—0.2) Monocytes 1.2 × 10^3/uL (ref. 0.1—0.9) Microfilaria seen	On admission: Total protein 7.5 g/dL (ref. 4.8—6.9) Globulin 4.4 g/dL (ref. 2.2—3.5) AST 118 U/L (ref. 21—53) ALT 150 U/L (ref. 14—87) ALP 174 U/L (ref. 20—157)	On admission: USG 1.030 Protein 1+
4	Unable to obtain at presentation	Unable to obtain at presentation	Unable to obtain at presentation

AST, aspartate aminotransferase; ALT, alanine transferase; ALP, alkaline phosphatase; PCV, packed cell volume.
The tests were performed either during initial hospitalization for intracardiac heartworms or within the preceding 3 weeks by the referring veterinarian. Only abnormal results are listed.

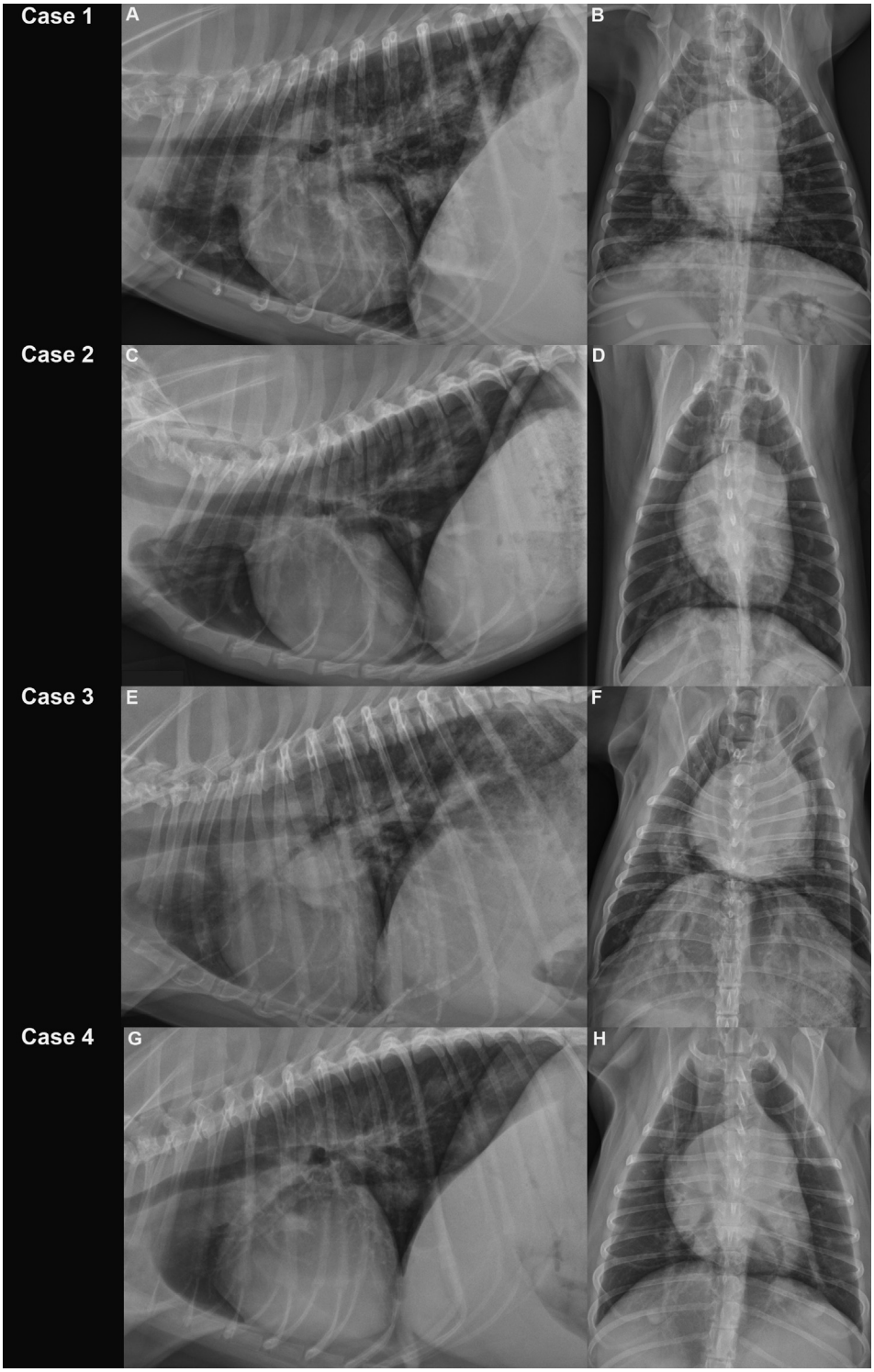

Figure 1 Thoracic radiographs performed in four dogs with intracardiac heartworms at initial presentation to the University of Wisconsin Veterinary Care. Case 1: left lateral (A) and ventral-dorsal (B) projections showing moderate enlargement of the right ventricle (RV) and right atrium (RA), severe enlargement of the main pulmonary artery (MPA), enlarged and tortuous pulmonary arteries, and patchy alveolar pulmonary infiltrates in the right caudodorsal lung field. Case 2: left lateral (C) and ventral-dorsal (D) projections showing mild enlargement of the RA, RV, and MPA, distended pulmonary arteries, and a mild diffuse interstitial pulmonary pattern. Case 3: left lateral (E) and ventral-dorsal (F) projections showing severe dilation of the MPA and severe enlargement of tortuous branch pulmonary arteries, most notable in the caudal lung fields. There is moderate enlargement of the RA and RV, and there is an interstitial to patchy alveolar pattern in the caudodorsal lungs. Case 4: left lateral (G) and ventral-dorsal (H) projection showing severe dilation of the MPA, enlarged and tortuous pulmonary arteries, moderate RA and RV enlargement, and a patchy interstitial pulmonary pattern.

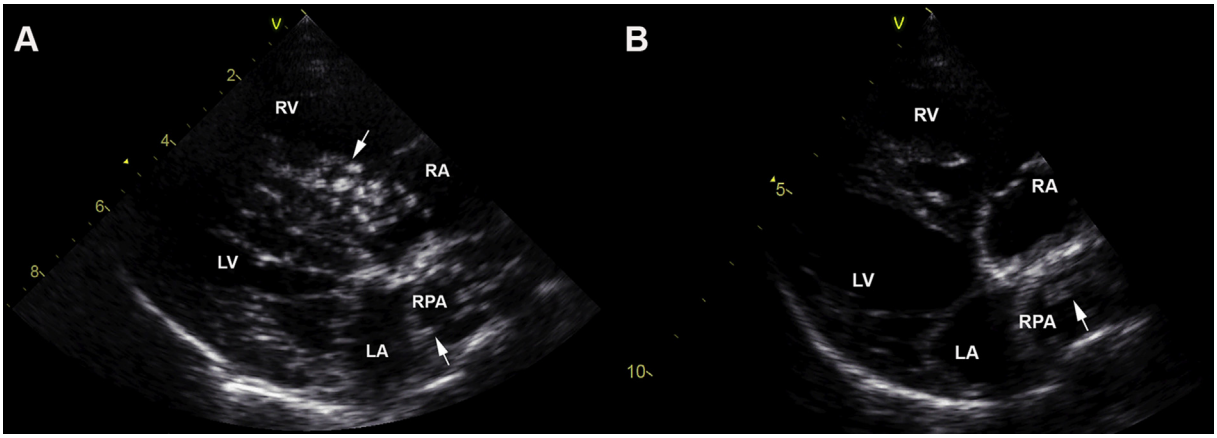

Figure 2 Two-dimensional echocardiography performed on the dog described in case 1 before and after receiving pimobendan and sildenafil. Images obtained from the right parasternal long-axis four-chamber view. (A) Heartworms were identified in the tricuspid valve apparatus and within the RPA (arrows) during the echocardiogram performed during the initial evaluation. (B) An echocardiogram was performed 48 h after starting treatment with standard doses of sildenafil and pimobendan. There were no heartworms identified in the tricuspid valve apparatus, RA, or RV. Heartworms remain within the RPA (arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

PCV had decreased further and was now 25% (reference 40—59%). Heartworms were still visible in the TV apparatus on echocardiogram. The sildenafil dose was increased to 2.1 mg/kg orally every 8 h, and the patient was prescribed pimobendan (0.35 mg/kg orally every 12 h). Surgical extraction via venotomy was scheduled for the next morning.

The next day, the patient was breathing comfortably and her PCV was static. She was anesthetized, and a transthoracic echocardiogram was repeated after induction, before jugular cutdown. The echocardiogram showed HWs in the MPA and not in the TV apparatus (Fig. 2B). The patient remained clinically stable over the next 24 h, and she was discharged from hospital the next day. A recheck evaluation was performed 1 week after original admission. Heartworms were identified in the MPA, but none were seen in the heart; there was no free peritoneal effusion, and the PCV was now within normal limits at 40% (reference 40—59%).

The patient received the first melarsomine injection (2.5 mg/kg IM) 3 days later. No intracardiac HWs were identified at this time. The patient remained hospitalized after the injection, and no complications were noted. One month later, at presentation for the second and third melarsomine injections, the owners reported that the dog was clinically normal with no respiratory signs. She presented 6 months later for follow-up and was clinically well and still receiving sildenafil and pimobendan. The results of the HW antigen test[a] were negative, and complete blood count and biochemistry results were normal. Echocardiography showed evidence of persistent but mild PH with a TR-estimated pulmonary pressure of 39 mmHg, moderate MPA dilation, and normal right-sided chamber sizes. After the results of this evaluation, all medications were discontinued. At last contact, the patient was reported to be doing well 33 months after initial presentation, with no clinical signs of PH or right-sided congestive heart failure.

Case 2

A 3-year-old male intact mixed breed dog presented for evaluation of HW disease and suspected caval syndrome (CS). He was identified to be HW positive when he presented to his veterinarian for pigmenturia a month earlier. The patient was evaluated by a veterinary cardiologist, and echocardiography showed HWs in his MPA, RV, and RA. He was not exhibiting clinical signs and was mildly anemic (PCV 31%, reference 40—59%). He was receiving doxycycline (5.0 mg/kg orally every 12 h) at presentation and had received one dose of moxidectin (25 mg orally).

At presentation, the patient was bright and his vital parameters were within normal limits. He had a grade 6/6 right apical systolic murmur and a grade 4/6 left apical systolic murmur. The remainder of the physical examination was within normal limits. Complete blood count results showed a mild macrocytic hypochromic regenerative anemia (PCV 34%, reference 40—59%) and moderate thrombocytopenia, and bilirubinuria was detected (Table 1). Thoracic radiographs showed

[a] Dirochek® Heartworm Antigen test kit, Zoetis, Parsippany, NJ, USA.

mild enlargement of the RA and RV, MPA enlargement, distended pulmonary arteries, and a mild diffuse interstitial pulmonary pattern (Fig. 1C and D). Echocardiography showed a large mass of HWs in the TV apparatus. The RV was mildly dilated, but there was no other evidence of PH as the TR-estimated pulmonary pressure was 30 mmHg, and the RA and MPA were normal in size. The patient was prescribed prednisone (0.5 mg/kg orally every 12 h), sildenafil (1.0 mg/kg orally every 8 h), and pimobendan (0.25 mg/kg orally every 12 h).

A recheck evaluation 1 week later showed that the HWs were now visible in the MPA and not in the TV apparatus and that the anemia had resolved (PCV 48%, reference 40—59%). The patient received the first melarsomine injection at that visit (2.5 mg/kg IM). The remainder of the treatment protocol followed the American Heartworm Society guidelines [1], and the patient remained asymptomatic during this time. He tested negative for HW antigen 6 months after receiving the last injection, and all the medications were discontinued. He was last evaluated 11 months after initial presentation, and he has remained asymptomatic.

Case 3

A 7-year-old male neutered pug presented to the referring veterinarian with an acute history of progressive exercise intolerance, tachypnea, and hyporexia. He was found to be positive on HW antigen testing.

On presentation, the dog was tachypneic and crackles were auscultated. His mucous membranes were pale and tacky. He had a grade 3/6 systolic right apical heart murmur. Initial blood work showed a moderate normocytic hypochromic anemia (Table 1). Thoracic radiography showed moderate right-sided heart enlargement, severe dilation of the MPA and branch pulmonary arteries, and an interstitial to alveolar pattern in the caudodorsal lung fields (Fig. 1E and F). Heartworms were identified in the TV apparatus using echocardiography, and there was evidence of severe PH, with a TR-estimated pulmonary pressure of 138 mmHg, moderate dilation of the RA, RV, and MPA, and moderate concentric RV hypertrophy. No free peritoneal fluid was found during a brief abdominal ultrasound. The patient was treated with sildenafil (1.3 mg/kg orally every 8 h), pimobendan (0.3 mg/kg orally every 12 h), dexamethasone SP (0.14 mg/kg IV every 24 h), doxycycline (8.8 mg/kg orally every 12 h), clopidogrel (1.7 mg/kg orally every 24 h), and ivermectin (136 mcg orally monthly). Echocardiography was repeated the next morning, and HWs remained visible within the RV, TV, and RA. The PCV had not changed but the dog's respiratory rate had improved. The sildenafil dose was increased to 1.8 mg/kg orally every 8 h. Echocardiography performed the next day showed that the HWs were only visible in the MPA. The patient remained hospitalized for a total of 5 days, during which time the respiratory rates had normalized and the PCV trended toward normal.

The dog presented for the first melarsomine injection 1 week later. He was reported to be doing well, but his liver enzymes were markedly elevated at this visit. This was suspected to be secondary to doxycycline-induced hepatotoxicity [2]. The first melarsomine injection (2.5 mg/kg IM) was administered 12 weeks after initial HW diagnosis, and the remainder of the treatment protocol was followed as per the American Heartworm Society guidelines [1]. The patient tested negative for HW antigen 6 months later at the referring veterinary clinic and then was lost to follow-up.

Case 4

A 3-year-old female spayed mixed breed dog presented with a history of suspected pulmonary thromboembolism. She had been diagnosed with HW disease 12 weeks earlier by her primary care veterinarian, and she had been treated with doxycycline (6.25 mg/kg orally every 24 h for 28 days) and selamectin (60 mg applied monthly to skin). She received the first injection of melarsomine (2.8 mg/kg IM) 3 weeks before the initial presentation. The patient was not showing clinical signs, and she was not strictly rested after this injection. One week after receiving melarsomine, she became acutely dyspneic. Thoracic radiographs were performed by the referring veterinarian and showed mild right-sided heart enlargement, pulmonary arterial distention, and a focal alveolar pattern in the caudal right lung lobe.

At presentation, 2 weeks after the acute dyspnea event, the dog had a grade 4/6 right apical systolic murmur and grade 5/6 left apical systolic murmur. Her vital parameters were normal, and she was eupneic. The remainder of the physical examination was within normal limits. The patient did not tolerate blood or urine collection. Thoracic radiographs showed moderate right-sided cardiomegaly, severe dilation of the MPA, enlarged and tortuous pulmonary arteries, and a patchy interstitial pulmonary pattern (Fig. 1G and H). The focal alveolar infiltrates, identified on the referring films performed 2 weeks earlier, had resolved.

On echocardiogram, HWs were identified in the MPA, RV, TV apparatus, and RA. There was evidence of moderate PH, including a TR-estimated pulmonary pressure of 69 mmHg, elevated pulmonic regurgitation—estimated mean pulmonary pressure (42 mmHg), moderate RV concentric hypertrophy, and moderate dilation of the RA, RV, and MPA. The patient was prescribed prednisone (0.6 mg/kg orally every 12 h), pimobendan (0.3 mg/kg orally every 12 h), and clopidogrel (2.3 mg/kg orally every 24 h). Sildenafil was recommended, and because caretakers could not medicate every 8 h, a dose of 1.9 mg/kg orally every 12 h was chosen.

A recheck evaluation was performed a week later and showed the HWs remained in the right-sided heart chambers and TV apparatus. Blood work was performed, and there were no significant abnormalities. The dosing frequency of both sildenafil and pimobendan was increased from every 12 h to every 8 h.

When the dog presented a week later for reassessment, HWs were identified in the MPA only. No changes to the treatment regimen were made at this time. The dog received the last two melarsomine injections with her primary care veterinarian. She presented 6 months after the last injection. She was found to be HW antigen negative at this visit, and she had evidence of mild to moderate PH on echocardiogram (TR-estimated pulmonary pressure 55 mmHg, mild RA dilation, moderate concentric RV hypertrophy, and moderate MPA dilation). All medications except monthly preventative doses of milbemycin oxime were discontinued. The patient was reported to be doing well 12 months after the initial presentation, with no clinical signs of PH. An echocardiogram performed at that time showed persistent mild PH, with a TR-estimated pulmonary pressure of 40 mmHg.

Discussion

Caval syndrome, also referred to as dirofilarial hemoglobinuria, is a severe manifestation of HW disease in which HWs become entangled in the TV apparatus, resulting in acute TR, compromised RV filling, microangiopathic hemolytic anemia, and hemoglobinuria [1,3—10]. These patients typically experience acute cardiovascular collapse, necessitating emergency stabilization [4—6]. Transvenous HW extraction is considered standard of care [4—6].

It remains unclear why some dogs develop intracardiac HW infections while others do not. While dogs with CS often have a high HW burden, this is not the sole predisposing factor [10]. Dogs with CS have a much larger proportion of the total worm burden redistributed to the RA, RV, and venae cavae compared with non-CS dogs [11]. Adult HWs live freely within the lumen of the pulmonary arteries, and their location within the vasculature is dictated by the volume and velocity of the blood flow [12,13]. Altered hemodynamic states, either due to increased vascular resistance or diminished cardiac function or both, may favor the development of CS [5]. Dogs with CS have significantly increased pulmonary arterial pressures (PAP) compared with non-CS dogs with equal HW burdens [10]. High PAP increases afterload, resulting in impaired RV filling and RV systolic and diastolic dysfunction [14]. Not all dogs with CS have severe PH [15], however, and the forward blood flow and subsequent HW migration may be due to a number of factors that vary between individuals, including acquired TR resulting from disruption of the normal biomechanical function of the TV, myocardial depression from enhanced parasympathetic tone or myocardial depression, and systemic vasodilation secondary to release of body fluid from dead HWs [9,12,13,16].

While many dogs with CS presented with signs of cardiogenic shock and multiorgan derangement, there are some dogs that appear to be less severely affected, despite the presence of intracardiac HWs. Cases 2 and 4 demonstrate that dogs can have imaging findings that are similar to dogs with CS, and yet their clinical signs are not as severe as expected for a dog with CS. In addition, some of the dogs reported here did not develop the typical biochemical hallmarks of progressive hemolytic anemia and hemoglobinuria. As a result, it may be inappropriate to apply the term CS to this manifestation of HW disease as the clinical presentation does not fit with the typical clinical course of CS. It is unclear as to why these dogs were less affected, and it may be due to a combination of lower HW burden, lower PAP, and/or less myocardial impairment.

In this case series, the HW moved from the right heart to the MPA in all four dogs after initiating sildenafil orally every 8 h and pimobendan orally every 12 h. The dog in case 1 was anesthetized for transvenous HW extraction, but surgery was ultimately aborted because the HWs were in MPA and out of reach of the intravenous retrieval tools available. It was unclear if the migration occurred after induction [4] or if was due to the effects of sildenafil and pimobendan. Emergency surgery was not attempted in the three remaining cases because either the HWs migrated into the MPA within 24 h of starting sildenafil and pimobendan (case 3) or the dogs were considered clinically

stable (case 2 and 4). In some cases in this report, the timing of the first melarsomine injection and the dose and duration of doxycycline differed from the recommended American Heartworm Society guidelines [1]. In addition, some medications were administered at off-label dosages. These decisions were made by the attending clinician based on the patients' clinical status.

Sildenafil is a phosphodiesterase type 5 inhibitor that induces pulmonary arterial vasodilation by enhancing nitric oxide—mediated relaxation [14,17]. It is possible that when used in dogs with intracardiac HWs, sildenafil helps to mobilize the HWs by decreasing PAP, which may contribute to improved cardiac output. There are few reports evaluating vasodilators in dogs with intracardiac HWs but hydralazine has been shown to significantly reduce PAP and pulmonary vascular resistance without significantly affecting the cardiac index in seven anesthetized dogs with experimentally induced HW disease [18]. It was suggested that the cardiac index did not change because these dogs had normal myocardial function, and therefore, reducing vascular impedance did not improve the stroke volume [18]. Sildenafil, on the other hand, has been shown to significantly decrease mean PAP and increase cardiac index in people with arterial PH from many causes [17]. Hemodynamic studies have not been performed in dogs that are treated with sildenafil for naturally occurring PH.

All the patients described here also received pimobendan therapy. Pimobendan improves inotropy and lusitropy by sensitizing myocardial contractile proteins to calcium and by acting as a phosphodiesterase type 3 inhibitor [19,20]. Inhibition of phosphodiesterase 3 receptors also results in vasodilation of the systemic and pulmonary vasculature [21]. Dogs with intracardiac HWs might benefit from pimobendan through reduction of PAP and improvement of RV myocardial function. Phosphodiesterase 3 and phosphodiesterase 5 receptors are upregulated in the pulmonary arteries in rats with experimentally induced PH, and therefore, using phosphodiesterase 3 and phosphodiesterase 5 inhibitors might result in a more profound reduction of PAP [21]. Dogs with intracardiac HWs may benefit from a positive inotropic agent because they develop RV myocardial dysfunction by multiple mechanisms, and decreasing PAP alone may not be enough to result in mobilization of intracardiac HWs.

It should be emphasized that while these dogs appeared to benefit from treatment with sildenafil and pimobendan, it remains unknown if medical management is efficacious and safe in dogs with intracardiac HWs that are clinically stable. This case series has not definitively shown that the HWs moved secondary to the effects of these medications, the number of patients is small, and there was no control group for comparison. Medications, cage rest, or changes in the clinical status may result in hemodynamic changes that favor HW movement from the heart to the pulmonary arteries [4,9,12,13]. Medical management is not appropriate in dogs that are progressively hemolyzing or experiencing acute cardiovascular collapse. In this study, no attempts were made to remove the HWs when seen only in the MPA; there is evidence that removing HWs from the MPA before adulticide therapy improves survival and rate of resolution of radiographic pulmonary alterations in dogs with severe HW disease compared with dogs treated with adulticide therapy alone [22]. The dogs reported in that study were not treated with doxycycline, which has been shown to reduce pulmonary pathology [23], and therefore, it is unknown if surgical extraction remains superior to adulticide therapy in dogs that were previously treated with doxycycline. Further controlled prospective studies are necessary to assess the efficacy and safety of sildenafil and pimobendan treatment before it can be recommended as a treatment for dogs with intracardiac HWs.

Conflicts of Interest Statements

The authors do not have any conflicts of interest to disclose.

References

[1] American Heartworm Society. Current canine guidelines for the prevention, diagnosis, and management of heartworm (Dirofilaria immitis) infection in dogs. Wilmington: American Heartworm Society; 2018.

[2] Schulz BS, Hupfauer S, Ammer H, Sauter-Louis C, Hartmann K. Suspected side effects of doxycycline use in dogs — a retrospective study of 386 cases. Vet Rec 2011; 169:229.

[3] Kitagawa H, Sasaki Y, Ishihara K. Clinical studies on canine dirofilarial hemoglobinuria: relationship between the presence of heartworm mass at the tricuspid valve orifice and plasma hemoglobin concentration. Jpn J Vet Sci 1986; 48:99—103.

[4] Bove CM, Gordon SG, Saunders AB, Miller MW, Roland RM, Achen SE, Drourr LT, Boggess MM. Outcome of minimally invasive surgical treatment of heartworm caval syndrome in dogs: 42 cases (1999-2007). J Am Vet Med Assoc 2010; 236:187—92.

[5] Strickland KN. Canine and feline caval syndrome. Clin Tech Small Anim Pract 1998;13:88—95.

[6] Kittleson MD, Kienle RD. Heartworm infection and disease (dirofilariasis). In: Kittleson MD, Kienle RD, editors. Small

Animal Cardiovascular Medicine. St Louis: Mosby; 1998. p. 370—401.
[7] Kitagawa H, Sasaki Y, Ishihara K, Kawakami M. Cardiopulmonary function values before and after heartworm removal in dogs with caval syndrome. Am J Vet Res 1991; 52:126—32.
[8] Kitagawa H, Kitoh K, Ohba Y, Kuwahara Y, Iwasaki T, Sasaki Y. Comparison of laboratory test results before and after surgical removal of heartworms in dogs with vena caval syndrome. J Am Vet Med Assoc 1998;213:1134—6.
[9] Kitagawa H, Sasaki Y, Ishihara K, Kawakami M. Heartworm migration toward right atrium following artificial pulmonary arterial embolism or injection of heartworm body fluid. Jpn J Vet Sci 1990;52:591—9.
[10] Atkins CE, Keene BW, McGuirk SM. Investigation of caval syndrome in dogs experimentally infected with *Dirofilaria immitis*. J Vet Intern Med 1988;2:36—40.
[11] Jackson RF, Otto GF, Bauman PM, Peacock F, Hinrichs WL, Maltby JH. Distribution of heartworms in the right side of the heart and adjacent vessels of the dog. J Am Vet Med Assoc 1966;149:515—8.
[12] Kitagawa H, Sasaki Y, Sukigara T, Ishihara K. Clinical studies on canine dirofilarial hemoglobinuria: changes in right heart hemodynamics inducing heartworm migration from pulmonary artery. Jpn J Vet Sci 1987;49:485—9.
[13] Kitagawa H, Ishihara K, Sasaki Y. Canine dirofilarial hemoglobinuria: changes in right heart hemodynamics and heartworm migration from pulmonary artery towards right atrium following β1-blocker administration. Jpn J Vet Sci 1987;49:1081—6.
[14] Gan CT-J, Holverda S, Marcus JT, Paulus WJ, Marques KM, Bronzwaer JGF, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Right ventricular diastolic dysfunction and the acute effects of sildenafil in pulmonary hypertension patients. Chest 2007;132:11—7.
[15] Kellum HB, Stepien RL. Sildenafil citrate therapy in 22 dogs with pulmonary hypertension. J Vet Intern Med 2007;21: 1258—64.
[16] Atkins CE, Keene BW, McGuirk SM. Pathophysiologic mechanism of cardiac dysfunction in experimentally induced heartworm caval syndrome in dogs: an echocardiographic study. Am J Vet Res 1988;49:403—10.
[17] Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148—57.
[18] Atkins CE, Keene BW, McGuirk SM, Sato T. Acute effect of hydralazine administration on pulmonary artery hemodynamics in dogs with chronic heartworm disease. Am J Vet Res 1994;55:262—9.
[19] Fitton A, Brogden RN. Pimobendan: a review of its pharmacology and therapeutic potential in congestive heart failure. Drugs Aging 1994;4:417—41.
[20] Solaro RJ, Fujino K, Sperelakis N. The positive inotropic effect of pimobendan involves stereospecific increases in the calcium sensitivity of cardiac myofilaments. J Cardiovasc Pharmacol 1989;14:S7—12.
[21] Murray F, MacLean MR, Pyne NJ. Increased expression of the cGMP-inhibited cAMP-specific (PDE3) and cGMP binding cGMP-specific (PDE5) phosphodiesterases in models of pulmonary hypertension. Br J Pharmacol 2002; 137:1187—94.
[22] Morini S, Venco L, Fagioli P, Genchi C. Surgical removal of heartworms versus melarsomine treatment of naturally-infected dogs with risk of thromboembolism. In: Seward RL, editor. Recent Advances in Heartworm Disease: Symposium '98. Batavia, IL: American Heartworm Society; 1998. p. 235—40.
[23] Kramer L, Grandi G, Passeri B, Gianelli P, Genchi M, Dzimianski MT, Supakorndej P, Mansour AM, Supakorndej N, McCall SD, McCall JW. Evaluation of lung pathology in Dirofilaria immitis-experimentally infected dogs treated with doxycycline or a combination of doxycycline and ivermectin before administration of melarsomine dihydrochloride. Vet Parasitol 2011;176:357—60.