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Sildenafil Citrate Therapy in 22 Dogs with Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is a disease condition characterized by abnormally increased pulmonary artery pressures and often is associated with a poor prognosis. Sildenafil is a phosphodiesterase inhibitor that causes pulmonary arterial vasodilation and reduction in pulmonary artery pressures.

Hypothesis: Treatment with sildenafil will improve echocardiographic determinants of PH in dogs, while also improving quality of life and survival.

Animals: Twenty-two dogs with clinical and echocardiographic evidence of pulmonary hypertension.

Methods: A retrospective study evaluating the effects of sildenafil on physical examination, ECG and radiographic findings, blood pressure and echocardiographic findings of PH, clinical score, and outcome was completed. PH was defined as a peak tricuspid regurgitation flow velocity ≥2.8 m/s or a peak pulmonic insufficiency flow velocity ≥2.2 m/s.

Results: Sixteen of 22 dogs with PH were elderly females of small body size. Their clinical score was significantly improved ($P = .0003$) with sildenafil treatment, but physical examination findings remained unchanged. Heart rate, respiratory rate, vertebral heart size, ECG heart rate, and systolic blood pressure did not change significantly with sildenafil treatment ($P > .05$). Peak tricuspid regurgitation flow velocities did not change significantly with the treatment of sildenafil, but selected systolic time intervals were significantly improved. Survival times for all dogs ranged from 8 to >734 days.

Conclusions and Clinical Importance: Sildenafil did not significantly lower the degree of measurable PH in dogs. Clinical improvement and increased quality of life was seen with sildenafil treatment, despite lack of significant change in other variables.

Key words: Echocardiographic; Heart disease; Pulmonary disease; Systolic time intervals.

Pulmonary hypertension (PH) is a persistent, abnormal increase in pulmonary systolic or diastolic pressure to greater than approximately 30/19 mm Hg.[1–5] PH in dogs can be primary (idiopathic) or secondary to various diseases, including vascular obliterative diseases such as dirofilariasis and pulmonary thromboembolism; primary structural pulmonary disease, such as pulmonary fibrosis, pneumonia, and neoplasia; hyperviscosity; reactive pulmonary arterial vasoconstriction; degenerative mitral valve disease and left-sided congestive heart failure (CHF); or congenital cardiac abnormalities, such as reversed patent ductus arteriosus (rPDA).[2–11] Doppler echocardiography provides a noninvasive and readily available method of diagnosing PH in conscious animals and is now the method of choice to diagnose naturally occurring PH in veterinary patients.[2–5,8]

The clinical presentation of dogs with symptomatic PH has been described anecdotally or in case series.[2,3,7,12] Echocardiographic and radiographic findings can be helpful to identify concurrent cardiac disease or pulmonary disease, and Doppler echocardiographic examination allows identification and indirect quantification of pulmonary arterial pressure by determination of peak tricuspid regurgitation flow velocity (PTRFV), peak pulmonic insufficiency flow velocity (PPIFV), or both, and subsequent estimation of pulmonary artery systolic and diastolic pressures.[2–5,8]

Sildenafil citrate (Viagra)[a] is a highly selective phosphodiesterase type V inhibitor that causes pulmonary artery vasodilation by increasing pulmonary vascular concentrations of cyclic guanosine monophosphate (cGMP). Increased concentrations of circulating pulmonary vascular cGMP cause vasodilation by increasing the activity of endogenous nitric oxide.[13] Little has been reported regarding the efficacy of sildenafil therapy or possible adverse effects in dogs with naturally occurring PH. The purpose of this study was to describe the presenting signs, clinical characteristics, and response to sildenafil therapy in 22 dogs with Doppler-echocardiographically diagnosed pulmonary hypertension of varying causes.

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Materials and Methods

Medical records from dogs at the University of Wisconsin Veterinary Medical Teaching Hospital Cardiology Service (2004–2006) were reviewed to identify dogs who received sildenafil to treat echocardiographically identified PH in the years 2004–2006. Thirty-eight dogs who received the drug to treat PH were identified. Dogs were required to have had at least one follow-up echocardiographic examination after at least 7 days of sildenafil therapy to be included in the study. Twenty-two dogs matching these criteria were identified and studied further.

The following information was extracted from the medical records: signalment, history; presenting complaint; heartworm status; physical examination findings; and diagnostic test results, including thoracic radiographs, Doppler-echocardiogram, 2-dimensional (2-D) echocardiogram, systolic blood pressure (SBP) measurement, ECG, CBC count, and serum chemistry evaluation when available. The final clinical diagnosis was recorded. SBP was measured via Doppler sphygmomanometry or oscillometric methods. Dogs who received antihypertensive medication other than angiotensin converting enzyme inhibitors were excluded from the SBP analysis. Dogs who received angiotensin-converting enzyme inhibitors were only included in the SBP analysis if the dose was unchanged between examination points. A standard 6-lead ECG was recorded with the dog in right lateral recumbency.

Thoracic radiographs were evaluated by a board-certified radiologist at the time of clinical evaluation. At the time of review, the presence and distribution of the pulmonary infiltrate pattern noted were recorded. Enlargement patterns were considered to be right-sided if any combination of main pulmonary artery, right

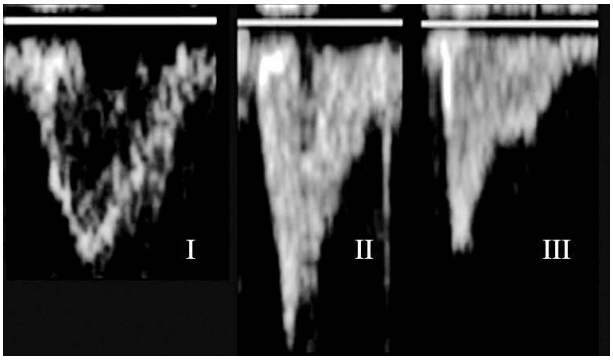

Fig 1. Pulmonary artery velocity flow profiles: type I (normal, a dome-like profile with the peak velocity flow occurring in the middle of systole with symmetric acceleration and deceleration phases), type II (the peak velocity flow occurring early in systole with a steep and rapid acceleration phase and slower deceleration phase), or type III (the same as type II but a notch occurs in the deceleration phase).

atrial, right ventricular, caudal vena cava, or hepatic enlargement were noted. Left-sided enlargement pattern was recorded if left atrial or left ventricular enlargement was noted. Pulmonary venous size was recorded as a separate variable, and other abnormalities were recorded.

Echocardiographic Examination

All echocardiographic examinations were reviewed by a single person (HBK). Full echocardiographic studies were performed at the time of original presentation in all dogs. Echocardiograms were repeated at least 7 days after initiation of sildenafil therapy. Standard 2-D views[14] and Doppler echocardiographic studies were performed by using a cardiac ultrasound unit.[b] Doppler evaluations were performed by using a 2.5- or 3-MHz transducer. The right- or left-sided view that allowed for optimal alignment of regurgitant flow (tricuspid regurgitation [TR] and pulmonic insufficiency [PI]) was used to measure instantaneous pressure gradients. Pulmonic stenosis was ruled out by evaluating for normal valvular anatomy and mobility on 2-D echocardiography and identification of laminar pulmonic flow profile via pulsed-wave Doppler echocardiography with peak pulmonary artery flow velocities less than 1.5 m/s. The modified Bernoulli equation (the change in pressure equals 4 times the velocity squared) was applied to the PTRFV and PPIFV to calculate the instantaneous right ventricular to right atrial and pulmonary artery to right ventricular pressure gradients, respectively. A PTRFV $\geq$2.8 m/s or peak TR flow gradient (PTRFG) $\geq$31.4 mm Hg or a PPIFV $\geq$2.2 m/s or a peak PI flow gradient (PPIFG) $\geq$19 mm Hg was considered to be abnormally high and indicative of PH.[2,4] Right atrial pressures were not measured or estimated in these dogs.

Pulmonary velocity flow profiles were subjectively evaluated and classified as either type I, II, or III (Fig 1).[2,4] Systolic time intervals (acceleration time [AT], ejection time [ET], AT : ET, pre-ejection period [PEP]) were measured as previously described by using a simultaneously recorded ECG.[4,15,16] The pulmonic AT was measured from the initial deflection of pulmonary blood flow profile to the peak flow. Systolic time interval variables were not corrected for heart rate.[4]

The right ventricle was evaluated subjectively for evidence of right ventricular hypertrophy and abnormal interventricular septal wall motion. The diameter of the main pulmonary artery (MPA) was evaluated as a pulmonary artery to aorta diameter ratio. MPA enlargement was noted if the pulmonary artery diameter exceeded the diameter of the aortic root in the same plane (right parasternal short-axis view). The timing and dose of sildenafil therapy was recorded. At follow-up, the dogs' owners' perception of clinical progress was recorded with the history, physical examination, and diagnostic test results after sildenafil therapy.

Clinical Score

All dogs received a composite clinical score at presentation and at follow-up at least 7 days later, based on (1) the presence of overt clinical signs, including exercise intolerance, respiratory distress, abdominal distension, or cough as assessed by the attending clinician based on a physical examination; and (2) the owner's general assessment of the dog's well being, including occurrence of syncopal episodes. Dogs with overt clinical signs significantly affecting quality of life received a clinical score of 2, dogs with identifiable clinical signs but moderate or mild impact on quality of life received a score of 1, and dogs with no clinical signs received a score of 0. The owner's assessment of general well being was based on owner's reports of activity levels, attitude, and appetite. The scores for both categories were added together (maximum score for worst affected dogs = 4) and recorded at presentation and at the first follow-up evaluation.

Dogs were categorized into 1 of 3 groups based on the confirmed or presumed etiology of PH. Group 1 (rPDA) included dogs with echocardiographically confirmed rPDA. Group 2 (respiratory disease) included dogs with PH that was attributed to respiratory disease and for which increased left atrial pressures were unlikely based on echocardiographic confirmation of normal left atrial size. Group 3 (heart disease) included dogs with PH that was attributed to severely increased left atrial pressures, as assessed by a left atrial : aortic ratio that exceeded 2.0 on echocardiographic examination. For the dogs in group 3, it was unclear if there were concurrent respiratory contributions to their PH.

The cause and date of death was ascertained by medical record review for dogs who did not survive at the end of the study period. Dogs still alive or euthanized for unrelated reasons were censored at the time of the end of the study period or date of euthanasia. For dogs euthanized for clinical signs related to PH, the date of euthanasia was considered equivalent to the date of death.

The following variables and findings were compared between presentation and follow-up: physical examination, composite clinical score, Doppler and 2-D echocardiographic values, SBP, thoracic radiographs, laboratory results, and ECG findings.

Statistical Analysis

Data analysis was performed with standard statistical software.[c] Because of small sample sizes, normal distribution could not be assumed and all variables were analyzed with nonparametric methods. A Wilcoxian signed rank test was used to compare values at baseline versus posttreatment. A Kruskal-Wallis test was used to compare the clinical score before and after sildenafil administration among the 3 subgroups. A decrease of $\geq$1 point on clinical score was classified as improvement at follow-up. P values $<$.05 were considered significant for all tests. Results are given as the median (range) for nonparametric values.

Results

Presentation

Of the 22 dogs included in the study, 15 were spayed females, 4 were neutered males, 1 was a sexually intact female, and 2 were sexually intact males. There was 1 mixed-breed dog, and the remaining 21 dogs were purebred, consisting of 3 West Highland White Terriers, 3 Miniature Poodles, 2 Maltese, 2 Yorkshire Terriers, 2

Scottish Terriers, and 1 dog each of the following breeds: Australian Cattle Dog, Japanese Chin, Rat Terrier, Norwich Terrier, Cavalier King Charles Spaniel, Welsh Terrier, Brittany Spaniel, American Water Spaniel, and Springer Spaniel. The age of the dogs at the time of diagnosis of PH ranged from 0.6 to 15.4 years (median, 12.5 years). The weight of the dogs at the time of diagnosis ranged from 2.4 to 21 kg (median, 8.0 kg).

Presenting Complaint

All dogs were examined because of referral for problems suspected to be cardiac or respiratory in origin. The most common presenting complaint was cough, reported in 17 dogs (77%). Also common were respiratory distress, ''raspy'' breathing, or referral for auscultated pulmonary crackles (n = 10 [45%]), lethargy (n = 7 [32%]), syncope or collapse episodes (n = 7 [32%]), or exercise intolerance (n = 5 [23%]). Five dogs had heart murmurs at the time of presentation but only 2 were examined for murmur evaluation without other complaints. Both of these dogs had rPDA as a final diagnosis. Two dogs were presented for evaluation of abdominal distention, ascites, or both. Most of the dogs had more than one presenting complaint (n = 16 [73%]). Sixteen dogs (73%) were given a clinical score of 4 at admission, 2 dogs (9%) had a score of 3, 3 dogs (14%) had a score of 2, 1 dog (5%) had a score of 1, and no dogs had a score of 0.

Physical Examination

Results of cardiac and respiratory auscultations were recorded in 20 dogs. Murmurs were auscultated in 16 of 20 dogs (80%). Three dogs had left-sided systolic murmurs only, 1 dog had a right-sided systolic murmur, and 12 dogs had systolic murmurs audible on both sides of the thorax. Three dogs had a normal cardiac auscultation, with abnormal respiratory sounds. Split or abnormally loud second heart sounds were auscultated in 4 dogs. Respiratory auscultation revealed pulmonary crackles (n = 14 [70%]), wheezes (n = 1 [5%]), and harsh or increased respiratory sounds (n = 4 [20%]). Normal respiratory findings were recorded in 4 dogs (20%). All 4 of the dogs with normal respiratory findings had heart murmurs noted. One dog was cyanotic. No dogs were in clinically evident CHF at the time of referral, but 7 (32%) were receiving various cardiac medications for previously diagnosed CHF, 6 dogs (27%) were receiving respiratory medications, and 4 dogs were receiving both cardiac and respiratory medications (18%). Five dogs (23%) were not receiving medications at the time of referral.

Diagnostic Test Results

Presenting ECG findings were available for 16 dogs. The most common ECG rhythm diagnoses were sinus arrhythmia (n = 6), normal sinus rhythm (n = 5), or sinus tachycardia (n = 4). Atrial fibrillation was present in 1 dog with severe mitral regurgitation and TR secondary to endocardiosis. One dog had an artificially paced rhythm at 80 bpm for concurrent persistent atrial standstill. One dog each had single atrial and ventricular premature complexes. Two dogs (both rPDA dogs) had a right axis deviation in the frontal plane.

Thoracic radiographs were performed in 20 dogs at presentation. The vertebral heart size was recorded in 18 dogs, and not all thoracic radiographs were available for review. MPA enlargement was noted in 6 dogs (30%). Pulmonary infiltrates were noted in 16 dogs (73%). Thirteen dogs had broncho-interstitial or interstitial pulmonary infiltrates, and broncho-alveolar or interstitial-alveolar infiltrates were noted in 3 dogs. Four of the 16 dogs had pulmonary infiltrates as the only abnormality noted. Less common abnormal pulmonary findings included narrow trachea (n = 2), atelectasis of 1 lung lobe (n = 1), a pulmonary mass lesion (n = 1), bronchiectasis (n = 1), and rounding of the lung lobes (n = 1).

Seven of 16 dogs with pulmonary infiltrates had combined left and right heart enlargement patterns, 3 dogs with pulmonary infiltrates had right-sided enlargement patterns only, and 2 dogs had left-sided enlargement patterns only. One dog of 16 with pulmonary infiltrates had pulmonary venous congestion, and this dog had severe cardiomegaly and previously diagnosed left-sided CHF. Four dogs had cardiac abnormalities without pulmonary infiltrates. Two of these dogs had both right- and left-sided enlargement patterns, and 2 had a right-sided enlargement pattern only. The latter 2 dogs were diagnosed with rPDA.

Pulmonary hypertension was diagnosed in 21 dogs based on the presence of high PTRFV and in 1 dog based on a high PPIFV. Nineteen dogs (86%) had mitral regurgitation attributable to chronic valvular disease or mitral valve dysplasia. Of these, 8 (42%) had moderate or severe degrees of mitral regurgitation with associated moderate-to-severe left atrial enlargement. TR was present in 21 dogs (95%). Based on their PTRFG, 7 dogs were categorized as having mild PH ($\leq$50 mm Hg), 7 dogs had moderate PH (51–75 mm Hg), and 7 dogs had severe PH (>75 mm Hg).[2] Subjective right-sided chamber dilation (atrial or ventricular) was noted in 14 dogs, and right ventricular wall thickening was present in 10 dogs. Systolic septal flattening was present in 6 dogs and paradoxic septal motion in 1 dog. PI was documented in 15 dogs. The median PPIFG was 29 mm Hg (range, 8–97 mm Hg). The single dog who was diagnosed based on PI alone had a PPIFG of 25 mm Hg (normal $\leq$19 mm Hg).[2]

Pulmonary artery flow profiles were evaluated in 21 dogs. Although 7 dogs had a PTRFV thought to represent mild PH, no dogs had a type 1 (normal) flow profile. Seven dogs had a type II profile, and 3 of these dogs had concordant gradients indicative of moderate PH. The remaining 13 dogs had type III flow profiles, and 5 of these had severe PH. Main pulmonary artery dilation was noted in 9 dogs. Systolic time intervals were evaluated in 21 dogs. SBP was recorded in 8 dogs and was abnormally high in 3 dogs.

Thirteen dogs had serum biochemical analysis. One dog had normal findings and various other single

Table 1. Comparison of selected physical and diagnostic test results before and after sildenafil therapy.

Variable	N	Before[a]	After[a]	*P* Value
Heart rate (beats per minute)	20	120 (60–200)	120 (60–168)	ns
Respiratory rate (breaths per minute)	8	32 (20–48)	30 (20–56)	ns
Clinical score	22	4 (1–4)	2 (0–4)	.0003
Systolic blood pressure (mm Hg)	5	143 (111–198)	125 (118–145)	ns
Vertebral heart size	9	12 (10–14.5)	11.75 (10–14)	ns
Peak TR flow gradient (all dogs, mmHg)	21	58 (35–169)	55 (30–179)	ns
Peak TR flow gradient (mm Hg) group 1 (rPDA)[b]	2	148 (128–169)	166 (152–179)	ns
Peak TR flow gradient (mm Hg) group 2 (respiratory disease)[b]	10	54 (35–106)	50 (33–106)	ns
Peak TR flow gradient (mm Hg) group 3 (heart disease)[b]	9	62 (39–131)	59 (30–77)	ns
PA AT (seconds)	14	0.05 (0.03–0.08)	0.06 (0.02–0.09)	.006
PA ET (seconds)	14	0.19 (0.13–0.25)	0.18 (0.14–0.22)	ns
PA AT : ET	14	0.30 (0.14–0.40)	0.34 (0.10–0.50)	.017
PEP (seconds)	12	0.05 (0.03–0.08)	0.04 (0.02–0.07)	.002
Peak PI flow gradient (mm Hg)	10	31 (10–97)	27 (8–89)	ns

ns, not significant; TR, tricuspid regurgitation; rPDA, reversed patent ductus arteriosus; PA, pulmonary artery; AT, acceleration time; ET, ejection time; PEP, pre-ejection period; PI, pulmonic insufficiency.

[a] Values are presented as median (range).

[b] See text for explanation of grouping variables

abnormal biochemical values were noted. The PCV was recorded in 8 dogs (including both dogs with rPDA) and was within expected normal range in all dogs. Heartworm status was known in 21 dogs; all were negative.

Group 1 (rPDA) included 2 dogs, group 2 (respiratory disease) included 11 dogs, and group 3 (heart disease) included 9 dogs.

Follow-up Examination

Clinical History/Response to Medication. The median number of days elapsed until first follow-up examination in all dogs was 31 (range, 7–521 days). The sildenafil dosages ranged from 2.08 to 5.56 mg/kg per day (median, 3.13 mg/kg). The appropriate sildenafil dose was reformulated and placed into capsules by the Veterinary Medical Teaching Hospital pharmacy for all dogs.

Physical Examination at Follow-up. Neither heart rate nor respiratory rate changed significantly with sildenafil treatment (Table 1). Results of cardiac and respiratory auscultations were recorded in 20 dogs, and no dogs had clinically significant changes in their murmurs or respiratory characteristics.

Clinical Score at Follow-up. There was a statistically significant difference in composite clinical scores at presentation and at follow-up ($P = .0003$). Total clinical score decreased by ≥2 in 14 dogs (64%), and 8 dogs had a clinical score of 0 after treatment. Clinical improvement was evident as increased activity, increased exercise ability, increased ease of breathing, improved demeanor, decreased ascites in affected animals, improved cough, and cessation or reduced frequency of syncopal or collapse episodes. There were no significant differences in change in the median clinical score among the 3 disease-based subgroups ($P = .17$). Most dogs (n = 15 [68%]) had no changes in medications, other than the addition of sildenafil, from the time of diagnosis to reevaluation, but 7 dogs had medications other than sildenafil added before reevaluation, including enalapril, furosemide, terbutaline, amlodipine, and doxycycline.

Adverse effects, which included lethargy, somnolence, clear nasal discharge, and erect ears, presumed to be the result of sildenafil therapy, were reported in 4 of 22 dogs (18%). No dog had sildenafil therapy discontinued because of clinical adverse effects.

Diagnostic Test Results. SBP did not differ significantly compared with presentation measurements (n = 5) at follow-up. Thoracic radiographs were performed in 9 dogs at follow-up. The vertebral heart size at follow-up (median, 11.8 vertebral lengths), did not differ from that at initial examination median value (Table 1). Pulmonary infiltrates were present in 5 of 9 dogs at follow-up (56%), and the degree and description of the infiltrates were unchanged between presentation and follow-up.

Echocardiographic examinations were recorded in 22 dogs after sildenafil treatment (selected findings Table 1). TR was present in 21 dogs after sildenafil treatment. The median PTRFG (55 mm Hg; range, 30–179 mm Hg) was unchanged from presentation measurements. No subgroups had detectable changes in median PTRFG compared with presentation. Septal flattening was no longer present in 4 of 6 affected dogs (Fig 2). The median PPIFG did not change after therapy (n = 10). Eight dogs had no categorical change in the flow profile category after therapy, 4 dogs improved by one category and one dog's profile worsened by one category. There was no difference in the median PTRFG change when dogs with an improved profile category were compared with dogs with worsening or no change in profile category ($P = .38$). Right ventricular systolic time intervals were evaluated in 14 dogs. There was a statistically significant increase ($P = .006$) in the median pulmonary AT after sildenafil therapy (Table 1). The AT : ET ratio was significantly increased (n = 14, $P = .017$), and the PEP was significantly

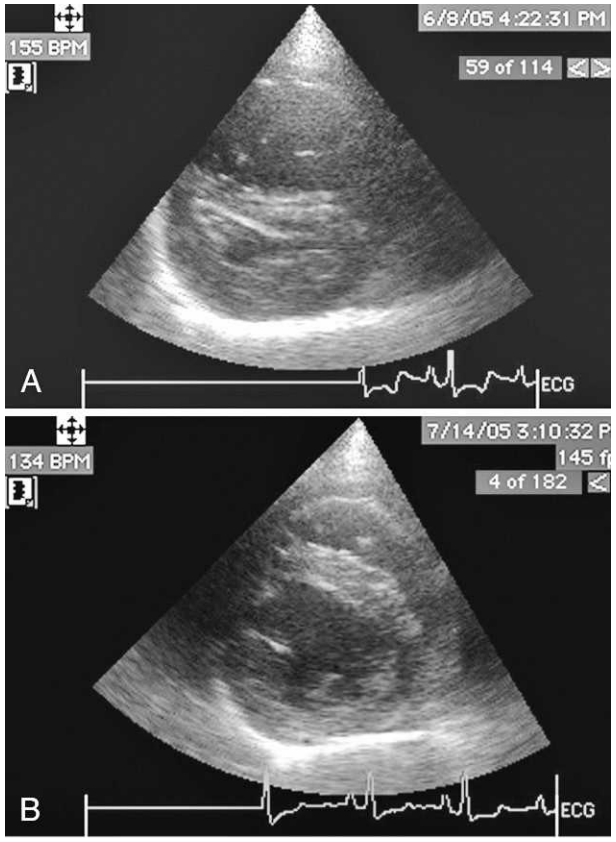

Fig 2. Echocardiographic views of a dog with pulmonary hypertension. **(A)** and **(B)** were obtained from the right parasternal short-axis view and are of the left and right ventricles at the level of the papillary muscles. Both images depict end-diastole. **(A)** Shows severe septal flattening at the time of diagnosis of PH. **(B)** Shows resolution of septal flattening after sildenafil therapy.

decreased (n = 12, P = .002). Twelve dogs had biochemical analysis at follow-up. No clinically important abnormalities were identified.

Outcome. Survival times ranged from 8 to >734 days (Fig 3). The median survival time for all dogs could not be calculated, because more than 50% of the dogs were alive at the end of the study period. The median follow-up of censored dogs was 247 days (range, 8–698 days). Ten dogs (45%) were euthanized or died by the end of the study period. Five of these dogs died of witnessed respiratory distress or were euthanized in extreme respiratory distress and were considered to have died or been euthanized because of their PH. Based on this series of 22 dogs with PH treated with sildenafil, if dogs survived the first week of therapy, the probability of survival to 3 months after initiation of therapy was 95%. There was an 84% probability of survival at 6 months and a 73% probability of survival at 1 year after initiation of therapy.

Discussion

Sildenafil was well tolerated in the dogs studied here, and both owners and veterinarians reported clinical

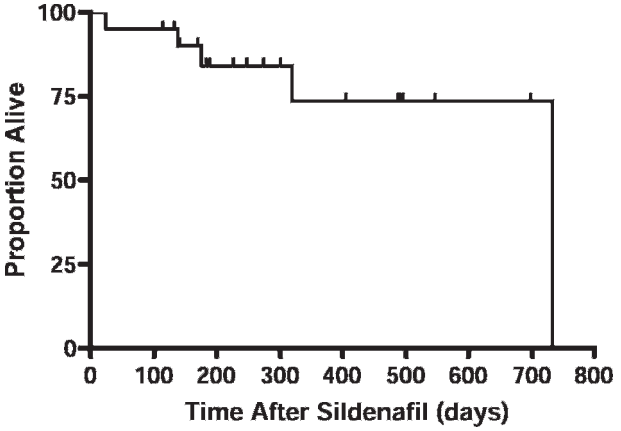

Fig 3. Kaplan-Meier curve of clinical outcome of 22 dogs with PH treated with sildenafil. Vertical ticks mark point of dog data censoring.

improvement in dogs who received sildenafil for PH. Improvement in clinical signs appeared to be the most reliable indicator of success of therapy. Other echocardiographic findings may support changes in pulmonary artery pressures, but the variability in Doppler gradient measurements may make PTRFV or PPIFV an unreliable indicator of success in a clinical population.

The majority of the dogs in this study of natural occurring PH were elderly females of small body size. Forty-five percent of the dogs in the study were terrier breeds. Chronic pulmonary diseases that predispose to PH are reported to be more common in terrier breeds,[12] but the predominance of female dogs in this study has not been previously reported.

In this study, the most common presenting signs were similar to previous reports and included cough, lethargy, syncope, and exercise intolerance.[1,3,5,10,17] However, 2 dogs were diagnosed after referral for evaluation of heart murmur alone. Both of these were young dogs diagnosed as having a rPDA and severe PH. In dogs with Eisenmenger's complex, severe PH is a result of pulmonary vascular obstructive disease rather than occurring in the presence of airway or pulmonary parenchymal disease.[18] This can account for the lack of the respiratory signs in the dogs with rPDA even though these signs were common in other dogs with PH. Signs of pulmonary vascular obstructive disease, such as cyanosis, exercise intolerance, and syncope, were not originally reported by the owners, but both dogs were noted by the owners to have increased activity levels while receiving sildenafil.

A review of these and previously reported findings suggests that there are no pathognomonic clinical signs or physical findings that can be used to diagnose PH with certainty. Populations at risk for PH often include dogs at risk for more common diseases with similar signs, including mitral insufficiency with CHF and chronic obstructive pulmonary diseases. More specific clinical history or findings suggestive of PH, including a history of syncope, the presence of TR murmurs, tachypnea, split or loud second heart sound, or cyanosis,[2,3,5,12] were recorded variably and often in the presence of more generic cardiorespiratory abnormali-

ties. Small-breed dogs with clinical signs and physical findings of cardiorespiratory disease might benefit from screening for PH, especially if syncope was reported. Results of this study suggested that successful treatment with sildenafil does not alter physical examination findings in dogs with PH and that a lack of change in physical findings did not predict a lack of clinical response to sildenafil. Abnormal physical examination findings in these dogs could have at least partially represented underlying cardiorespiratory abnormalities and might not be expected to change with sildenafil treatment.

Clinical scores at initial examination represented a range of severity of clinical signs. All dogs had some indication of impairment of daily activity. After treatment, the median clinical score improved significantly, and 8 dogs had a clinical score of 0 (no clinical signs) after therapy. These findings might reflect the improved pulmonary hemodynamics and functional capacity with regression of right ventricular hypertrophy[19] and is in agreement with previous studies of dogs[3] and people.[19–22] The possibility that PH could have been associated with an acute, potentially transient event, such as pulmonary thromboembolism might explain an apparent treatment effect. Group 3 dogs could have improved because of the instigation of furosemide therapy and subsequent resolution of pulmonary edema. The clinical scoring system used in this study was meant to reflect owner-assessed changes, as well as clinical changes recorded by the attending clinician. Though crude, the score was able to reflect the significant changes in quality of life experienced by many of these dogs. Although there were too few dogs in group 1 to assess, disease groups 2 and 3 did not differ in their response to sildenafil in terms of clinical score. This might indicate that the etiology of PH is not necessarily a predictor of response to sildenafil therapy or could reflect the difficulty of separating dogs with primary pulmonary disease and those with both cardiac and pulmonary disease. A clinical score improvement was fairly consistent, despite a lack of a significant change in PTRFG and PPRFG in response to therapy, possibly reflecting the variability in Doppler echocardiographic measurements based on Doppler interrogation beam alignment.

Thoracic radiographs did not significantly change with sildenafil treatment. Cardiomegaly and pulmonary infiltrates were common and nonspecific findings, and most dogs with PH did not have enlarged pulmonary arteries noted. Although thoracic radiographic assessment of PH is frequently complicated by changes associated with concurrent cardiopulmonary disease processes, the presence of pulmonary infiltrates without pulmonary venous enlargement was a consistent finding and may lead the clinician to consider PH as a differential diagnosis in a dog who is dyspneic.

Peak flow velocity and associated gradients of TR or PI were used to diagnose PH in this study. This method allows rapid, noninvasive estimation of pulmonary pressures in dogs, but accuracy of predicted pressure gradients depends on operator skill and experience and the ability of the dog to tolerate the examination. The addition of the right atrial pressure (if known) to the TR gradient theoretically provides the most accurate prediction of pulmonary systolic pressure,[4,23] but right atrial pressure is not routinely measured in dogs. Because of the innate error in estimations of right atrial pressure and because only one dog was diagnosed as having right heart failure based on clinical signs, the PTRFG alone was used to diagnose systolic PH.

Pulmonary artery pressures assessed by TR and PI did not change significantly after sildenafil treatment as a whole or by disease subgroup. This differs from the findings in a recent study[3] and studies performed in humans,[19–22] which have a significant reduction of pulmonary artery pressure when treated with sildenafil. In conscious dogs who were dyspneic, difficulty in obtaining repeatable, precise measurements of PTRFV jets could limit documentation of response to therapy, and other clinical findings should be taken into account when evaluating the response to sildenafil treatment.

Pulmonary artery flow profiles have been used in dogs and humans to estimate the severity of the PH.[2,4,6,15–17,24] In this study, the pulmonary artery flow profile categorizations did not always correctly associate with the severity of the calculated gradient at presentation. Nonetheless, the lack of normal pulmonary artery flow profiles recorded at presentation suggested that identification of an abnormal flow profile may be potentially valuable in supporting a diagnosis of PH, but the usefulness of this variable to monitor the effects therapy was not apparent in this study.

Right ventricular systolic time intervals have been used to support the diagnosis of PH in dogs[4,16] and people.[15,25] Here, right ventricular AT, AT : ET, and PEP were reduced compared with normal at presentation, consistent with PH.[4,15,16,25] Values of ≤ 0.31 for the AT : ET and an AT value of ≤ 0.058 seconds were predictive of PH,[4] and these values might be useful to diagnose PH in animals without insufficiency jets. Although the median AT : ET of 0.30 and AT of 0.050 seconds falls within the range consistent with PH by these diagnostic cutoff values, 43% of AT : ET ratios were >0.31 and 38% of AT were >0.058 seconds, demonstrating the variability of this parameter when used in dogs with Doppler-demonstrated PH of various etiologies. Although the change in systolic time intervals for the group was statistically significant, the reduction in PEP and the increase in AT was small (0.01 seconds). These changes may not impart clinical significance, and the range precludes its application in assessing response in an individual dog.

Etiologic categorization of group 1 and 2 dogs was relatively straightforward, but the third group was more ambiguous. Three of the category 3 dogs had moderate-to-severe mitral regurgitation, pronounced pulmonary crackles on physical examination, and pulmonary infiltrates on thoracic radiographs, but no evidence of pulmonary venous enlargement. These animals were suspected to have concurrent cardiac and pulmonary disease as the cause of PH, but there was no histopathologic confirmation. Pulmonary artery pres-

sures >40 mm Hg were suspected to represent more than left heart failure alone (n = 19), but pulmonary artery pressures in excess of left atrial pressures may occur in dogs with PH secondary to left heart failure if reactive PH because of hypoxia is present.[11,26]

Clinically apparent adverse effects of sildenafil were uncommon in this population and did not necessitate drug discontinuation in any dog, but dogs were often receiving multiple medications at the time of appearance of clinical signs, making it difficult to attribute adverse effects to sildenafil alone. No biochemical abnormalities could be directly correlated with sildenafil therapy.

There were a number of limitations of this study. A small number of dogs were available for review, especially when subgroups were studied. There was no standard diagnostic workup for these dogs, which resulted in incomplete diagnostic testing and results. The number of blood pressures measurements performed was small, which made it difficult to evaluate the systemic effects of a medication with the potential to cause hypotension. A variable echocardiographic technique made echocardiographic results potentially less consistent over time. Lastly, dogs who did not appear for reevaluation after therapy were excluded from the study. This action could have excluded dogs who are severely ill and poor responders, but also could have included dogs who responded very well and continued to obtain medication elsewhere.

Footnotes

[a] Viagra, Pfizer U.S. Pharmaceuticals, New York, NY
[b] Vivid 5 and Vivid 7, General Electric Medical System, Waukesha, WI
[c] Prism 4.0a for Macintosh, Graphpad Software Inc, San Diego, CA

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