Retrospective Evaluation of Clinical Parameters and Survival Characteristics in 137 Dogs with Reversed Patent Ductus Arteriosus

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By

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The undersigned, appointed by the Dean of the Graduate School, have examined the thesis entitled

Retrospective Evaluation of Clinical Parameters and Survival Characteristics in 137 Dogs with Reversed Patent Ductus Arteriosus

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A candidate for the degree of Master of Science,

And hereby certify that, in their opinion, it is worthy of acceptance.

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1. Body conditions score (BCS)
2. Congenital heart disease (CHD)
3. Confidence interval (CI)
4. Eisenmenger's syndrome (ES)
5. Hazard ratio (HR)
6. Median survival time (MST)
7. Muscle condition score (MCS)
8. Packed cell volume (PCV)
9. Patent ductus arteriosus (PDA)
10. Patent foramen ovale (PFO)
11. Phosphodiesterase-V inhibitor (PDEVi)
12. Pulmonary arterial hypertension (PH)
13. Right-sided congestive heart failure (rCHF)
14. Reversed patent ductus arteriosus (rPDA)
15. Right ventricle (RV)

ABSTRACT

Background: Reversed patent ductus arteriosus (rPDA) is a comparatively rare form of canine congenital heart disease (CHD) and is defined by severe pulmonary arterial hypertension (PH), pulmonary-to-systemic shunting across a patent ductus arteriosus (PDA), caudal hypoxemia, and secondary erythrocytosis. These aberrations of normal structure and physiology dictate the phenotype of dogs with rPDA. To date, the veterinary literature contains a limited number of case reports and a single retrospective study of 43 dogs with rPDA.

Objectives: This multi-center, retrospective descriptive study details patient characteristics, clinical signs, diagnostic findings, and survival data that typify rPDA in a large number of dogs.

Animals: Dogs (n=137) diagnosed with rPDA by a board-certified cardiologist or a resident under the direct supervision of a board-certified cardiologist were retrospectively enrolled.

Methods: Medical records of dogs diagnosed with rPDA between 5/1/1980 and 12/1/2019 were retrospectively reviewed at 19 centers in North America, Europe, and Asia. Demographic information and clinical data were collected and analyzed statistically.

Results: Female dogs were overrepresented, accounting for 65% of the study population. Mean (+/- standard deviation) age at presentation was 29.1 months (+/-27.7). At the time of initial evaluation, 93% of dogs were exhibiting clinical signs, with exercise intolerance being most common. Right-sided congestive heart failure (rCHF) was diagnosed infrequently (15%). The mean maximum PCV was 66.6% (+/-12.0). Common echocardiographic findings included abnormal interventricular septal motion (88%), tricuspid valve regurgitation (69%), and right ventricular (RV) concentric hypertrophy (62%). Most dogs (67%) received a phosphodiesterase-V inhibitor (PDEVi), and phlebotomy was performed at least once in 41% of dogs. In bivariate survival analysis, the median survival time (MST; 95% confidence interval) was 90.6 months (74.4-121.9) for dogs that received a PDEVi versus 18.6 months (5.8-88.0) for those that did not ($p= 0.008$); 123.1 months (87.8-132.5) for those that received hydroxyurea versus 73.9 months (40.0-90.2) for those that did not ($p= 0.008$); and 112.4 months (74.4-129.1) for those that were treated with therapeutic phlebotomy versus 83.8 (36.9-90.2) for those that were not ($p< 0.001$). These factors remained significant predictors of survival in a multivariate analysis. Older age at presentation ($p< 0.001$), presenting PCV< 65% ($p= 0.005$), and absence of rCHF ($p= 0.047$) were also associated with improved survival in the multivariate analysis.

Conclusions: The clinical, physical examination, and diagnostic findings associated with rPDA in 137 dogs were characteristic of severe pulmonary hypertension, chronic hypoxemia, and polycythemia. Phlebotomy, PDEVi therapy, and hydroxyurea, were

associated with longer survival times. Conversely, survival times declined with rCHF and younger age at presentation.

Chapter 1

INTRODUCTION AND LITERATURE REVIEW

1.1 A review of circulatory alterations at parturition

During prenatal life, oxygen is obtained via the fetal membranes rather than by alveolar ventilation.[1,2] Thus, blood returning to the right heart via the umbilical vein is relatively well-oxygenated. The normal arrangement of fetal circulation permits this oxygen-rich blood to be diverted away from the pulmonary vascular beds via the foramen ovale and ductus arteriosus. The latter represents a normal communication between the main pulmonary artery and the descending aorta. Given the high pulmonary vascular resistance that exists during fetal development, pulmonary-to-systemic flow predominates. Similarly, pressure within the right atrium normally exceeds that within the left atrium. This induces right-to-left flow across the foramen ovale, which is located within the interatrial septum.

Abrogation of the placental circulation at parturition results in a marked increase in systemic vascular resistance.[1,2] Pulmonary vascular resistance declines as the lungs are inflated and the pulmonary arterioles dilate. Ultimately, systemic arterial pressure exceeds that of the pulmonary arteries, altering the direction of flow across the ductus.[1-3] Simultaneously, arterial oxygen tension increases and local prostaglandins are suppressed. These alterations promote constriction of mural smooth muscle within the ductus arteriosus, thereby instigating functional closure.[1,2,4,5]

As systemic pressure rises and pulmonary arterial pressure decreases, the pressure differential between the left and right atrium reverses. This causes functional closure of

the foramen ovale via a membranous valve. Collectively, these changes culminate in the transition to post-natal circulation, which is normally characterized by two distinct circulations arranged in series.[1,2]

1.2 Pathophysiology of patent ductus arteriosus.

Various pathophysiologic mechanisms may conspire to sabotage functional closure of the ductus arteriosus.[3,5,6] This phenotype is termed a patent ductus arteriosus (PDA). Previous studies have demonstrated an abnormal distribution and/or a paucity of ductal smooth muscle in dogs with PDA.[4] This is a heritable condition in dogs and is transmitted as a threshold or polygenic trait.[7]

In mammals, pulmonary vascular resistance falls precipitously at the time of parturition due to ventilation of the lungs, pulmonary oxygenation, and attendant vasodilation of the pulmonary arteries.[1-3] Not only does this enable normal post-natal perfusion of the lung, but in conjunction with an increase in systemic vascular resistance (see section 1.1), it establishes systemic-to-pulmonary ductal flow in patients with PDA.[1,2,4,7]

The hemodynamic significance of a PDA is determined by the shunt volume.[5] In a dog with a shunt of sufficient magnitude, chronic systemic-to-pulmonary flow across a PDA imposes a pathological increase in left ventricular preload.[6] Left-sided congestive heart failure is a life-limiting sequela of PDA in a majority of dogs.[6-8] In one study of 520 dogs with PDA, median survival time was 2 years for animals that did not undergo surgical or trans-catheter closure.[9]

1.3 Pulmonary hypertension associated with congenital cardiac shunts

By virtue of pulmonary over-circulation and increased endothelial shear stress, there is a recognized association between left-to-right congenital cardiac shunts and pulmonary arterial hypertension (PH).[7,8,10-14] Endothelial dysfunction and disruption of the nitric oxide, thromboxane, prostacyclin, and endothelin signaling pathways, among others, promote vasoconstriction and chronic vascular remodeling.[5,14] Specifically, inflammation, medial hypertrophy, and intimal proliferation collectively increase pulmonary vascular resistance, a defining feature of pre-capillary PH.[5,12,13]

This scenario is distinct from post-capillary pulmonary hypertension, in which increased pulmonary artery pressure is a corollary of elevated left atrial pressure. However, both phenomena can occur concomitantly in patients with uncorrected left-to-right cardiac shunts.[12,13,15] Severe PH is evidenced histologically by the presence of plexiform lesions. These vascular abnormalities are the irreversible hallmark of World Health Organization Group 1 PH, which includes PH associated with congenital cardiac shunts.[11,16] The ACVIM Consensus statement pertaining to canine pulmonary hypertension similarly identifies PH associated with congenital cardiac shunts as a subcategory of Group 1 PH (Group 1d1).[12] Eisenmenger's syndrome is the most advanced clinical manifestation of PH in patients belonging to Group 1d1, and its defining attribute is shunt reversal due to suprasystemic pulmonary vascular resistance.[5,14,17]

1.4 Pathophysiology of reversed patent ductus arteriosus in the dog

Reversed PDA (rPDA) is a rare clinical entity that occurs in dogs that have both a PDA and suprasystemic pulmonary vascular resistance.[6,7] If severe PH is the result of the shunt, and by extension, chronic pulmonary over circulation, the eponym 'Eisenmenger's syndrome (ES)' can be applied.[5,614,17] However, suprasystemic pulmonary pressure can occur as a consequence of other conditions. Persistent pulmonary hypertension of the newborn (formerly persistence of fetal circulation) is an alternative cause of postnatal PH in which abnormal pulmonary vascular resistance may be due to acute hypoxia-mediated vasoconstriction, remodeling of the pulmonary vasculature, lung hypoplasia, or intravascular obstruction.[3,18] This syndrome can also cause right-to-left shunting if an anatomical substrate exists.

The aberrations of physiology and anatomy that define rPDA also readily account for the clinical phenotype of affected dogs.[6,12] De-oxygenated blood from the pulmonary artery is diverted to the descending aorta, resulting in differential cyanosis.[5,6,19] Patients exhibit exercise intolerance, pelvic limb weakness, and syncope.[6,12,19]

In response to chronic hypoxemia, the kidneys increase production of erythropoietin, thereby attempting to generate a compensatory expansion of oxygen carrying capacity.[17,20] However, the resultant increase in PCV can become maladaptive, leading to hyperviscosity syndrome and increased risk of thrombosis.[6,17]

Right heart failure is apparently uncommon in dogs with rPDA.[6,19,21,22] However, lifespan is often reduced, with a recent retrospective study reporting an overall median survival time (MST) of 626 days (range 1-3628).[19]

1.5 Clinical management of reversed patent ducuts arteriosus

Various treatments have been reported for the clinical management of dogs with rPDA. Therapies are targeted to ameliorate pulmonary hypertension, chronic hypoxia, and polycythemia.[21-23] Classically, phlebotomy has been considered a fundamental strategy for managing patients with ES.[6,21] This treatment may be performed when the PCV exceeds 65% but is typically only advocated when dogs are exhibiting corresponding clinical signs. The purpose of this judicious approach is to limit fluctuations in blood volume and oxygen carrying capacity.

Hydroxyurea provided a viable alternative to phlebotomy in a case series of 4 dogs with rPDA.[22] This is an antineoplastic DNA synthesis inhibitor that has been used to address polycythemia in companion animals.

Sildenafil is a phosphodiesterase-V inhibitor (PDEVi) that has been employed for management of pulmonary hypertension in dogs.[15,24-26] By antagonizing the action of phosphodiesterase V, sildenafil yields increased levels of cyclic guanylate monophosphate within vascular smooth muscle.[12,16,24] This augments the capacity for endogenous nitric oxide, which activates cyclic guanylate monophosphate, to effect pulmonary arterial vasodilation. A case series described the effects of sildenafil therapy in 5 dogs with ES.[23] The packed cell volume (PCV) of all dogs decreased significantly relative to baseline following 3 months of treatment, and each dog achieved a PCV of <65%. Previous studies investigating the efficacy of sildenafil in dogs with pulmonary hypertension have reported improvement in clinical status and quality of life.[24,25] Additionally, a recent retrospective study involving 43 dogs with rPDA determined that there was a statistically significant difference in survival between dogs that received a

PDEVi and those that did not. Survival was comparatively increased for the latter group.[19]

In human patients with ES, PDEVi medications are recommended as a first-line therapy for amelioration of PH.[17] Alternatively, endothelin-1 antagonists can be implemented for initial monotherapy, and prostacyclins can be added for multi-modal treatment. The current ACVIM consensus statement on canine pulmonary hypertension does not advocate for the use of endothelin-1 antagonists or prostanoids in dogs, as there is a paucity of data in the veterinary literature concerning their safety and efficacy.[12] Further, these agents tend to be cost-prohibitive and/or require methods of administration that may be impractical.[15]

Conventional wisdom dictates that ductual closure is contraindicated in patients with ES and unidirectional right-to-left shunting.[12,16,27] In the aforementioned retrospective report of 43 dogs with rPDA, ductal closure was successful in two dogs with bi-directional shunting.[19] Both animals received a PDEVi prior to closure.

1.6 A brief review of cardiac cachexia

Cachexia is defined as a reduction in muscle mass due to a disease state and can occur in patients with a decreased, normal, or increased body habitus.[28] Previous studies have demonstrated that cachexia is associated with decreased median survival time in companion animals with congestive heart failure.[29-31] Some of these investigations have determined that survival is correlated with muscle condition score but not BCS, while others have indicated that survival time declines in patients with low BCS when compared to patients with increased BCS.

Further, a study evaluating the muscle condition score for assessment of muscle mass in dogs noted that BCS correlated with muscle condition score. However, the investigators cautioned that the two parameters are not directly related.[28] Overall, these studies indicate that muscle condition score is the superior metric for identifying cachexia in companion animals with congestive heart failure.[29-31]

1.7 Objectives

A number of case reports and case series pertaining to rPDA have been published in the veterinary literature, and to date, there has been only one moderately-sized retrospective study [Buchanan/Patterson].[7,19,21-23,32-35] However, this is unlikely to adequately define the quintessential manifestations and natural history of spontaneously occurring rPDA in companion animals. The objective of this thesis is to retrospectively describe the patient characteristics, clinical signs, diagnostic findings, and survival data that typify rPDA in a large number of dogs.

Chapter 2

RETROSPECTIVE EVALUATION OF CLINICAL PARAMETERS AND SURVIVAL CHARACTERISTICS IN 137 DOGS WITH REVERSED PATENT DUCTUS ARTERIOSUS

2.1 Introduction

The reported prevalence of congenital heart disease (CHD) in the general canine population is 0.13-0.89%, while developmental lesions account for approximately 16.4-21.7% of all cases referred for cardiovascular evaluation.[1-5] Left-to-right shunting patent ductus arteriosus (PDA) is consistently ranked among the most common congenital cardiac anomalies in dogs, representing 20-30% of defects.[2,4-6] Conversely, right-to-left shunting or reversed PDA (rPDA), though a recognized cause of cyanotic heart disease, is apparently rare.[1,7] In a retrospective study of canine CHD involving 76,301 mixed breed dogs, 105 cardiac lesions were identified. However, there was only 1 instance of rPDA.[5] In a separate study, 237 of 4,480 dogs were diagnosed with a PDA, though only 6 exhibited the reversed PDA phenotype.[3] A recent retrospective epidemiological study conducted in Italy reported that rPDA was diagnosed in only 0.7% of dogs with CHD[8].

The normal arrangement of the prenatal circulation permits relatively oxygen-rich blood derived from the fetal membranes to be diverted away from the pulmonary vascular beds via the ductus arteriosus.[9,10] The latter represents a communication between the main pulmonary artery and the descending aorta, and given the high pulmonary vascular resistance that exists during normal fetal development, pulmonary-to-systemic flow predominates. At birth, systemic vascular resistance increases due to abrogation of the placental circulation, causing systemic pressures to exceed pulmonary pressures.[9-11]

Simultaneously, closure of the ductus arteriosus is instigated by an increase in oxygen tension and suppression of local prostaglandins, resulting in vasoconstriction of mural smooth muscle within the vessel.[9,10,12,13]

Various pathophysiologic mechanisms may conspire to sabotage functional closure, resulting in a PDA.[1,11-13] In dogs, this occurs due to an abnormal distribution and/or a paucity of ductal smooth.[12] In mammals, pulmonary vascular resistance falls precipitously at the time of parturition due to ventilation of the lungs, pulmonary oxygenation, and attendant vasodilation of the pulmonary arteries.[9-11] Not only does this enable normal post-natal perfusion of the lung, but in conjunction with the aforementioned increase in systemic vascular resistance, it establishes systemic-to-pulmonary ductal flow in patients with PDA.[1,7,9,10,12]

As the term suggests, rPDA is defined by intermittent or continuous flow in the opposite orientation (pulmonary-to-systemic).[1,6,7] Pulmonary vascular resistance must supersede systemic resistance for this phenotype to persist or arise postpartum.[1,7,11,14-19] In human patients with large congenital cardiovascular shunts, the eponym 'Eisenmenger's syndrome (ES)' is applied to describe the most advanced manifestation of pulmonary arterial hypertension (PH), which culminates in right-to-left shunting.[1,13-15] In this scenario, PH is attributable to an antecedent left-to-right cardiovascular shunt and, by extension, chronic over-circulation of the pulmonary vasculature.[13-16,18,20,21] Eisenmenger's syndrome is clinically characterized by systemic hypoxia and secondary polycythemia. Persistent PH of the newborn (formerly persistence of fetal circulation) is an alternative cause of postnatal PH in which abnormal pulmonary vascular resistance may be due to acute hypoxia-mediated vasoconstriction, remodeling of the pulmonary

vasculature, lung hypoplasia, or intravascular obstruction.[11,19] This condition can, similarly, promote right-to-left shunting across an anatomical substrate such as a PDA or patent foramen ovale (PFO).

A number of case reports and case series pertaining to rPDA have been published in the veterinary literature.[7,22-28] However, such reports are unlikely to adequately define the quintessential manifestations and natural history of spontaneously occurring rPDA in companion animals. To date, there is a single retrospective study chronicling the clinical attributes of 46 affected dogs and cats.[29] The objective of the current multi-center, retrospective descriptive study is to detail the patient characteristics, clinical signs, diagnostic findings, and survival data that typify rPDA in a large number of dogs from geographically diverse regions.

2.2 Materials, and Methods

For the purpose of this retrospective descriptive study, participation was solicited from board-certified cardiologists located throughout the United States, Europe, and Asia. Clinicians affiliated with both academic institutions and private practice centers were contacted. Correspondence achieved using information available in the American College of Veterinary Internal Medicine and Veterinary Information Network electronic mailing directories. Analog and electronic medical records of participating centers were queried to identify dogs diagnosed with rPDA or bidirectional PDA. Dogs were included if the diagnosis was conferred by a board-certified cardiologist or a resident under the direct supervision of a board-certified cardiologist between the dates of 5/1/1980 and 12/1/2019.

Signalment, presenting clinical signs, physical examination findings, initial and final body condition score (BCS) on a scale of 1-9, echocardiographic and radiographic results, electrocardiographic diagnosis, presenting and maximum packed cell volume (PCV) or hematocrit, cardiac comorbidities, lifetime occurrence of right-sided congestive heart failure (rCHF), pharmacotherapy, instances of phlebotomy, and survival status were retrieved from the medical records.[30,31]

Patient records were reviewed to confirm the imaging modality employed for diagnosis. Two-dimensional echocardiographic measurements of the left ventricle and left atrium obtained from the right parasternal transverse and longitudinal imaging planes, respectively, were normalized to body weight using previously published allometric scaling exponents.[32,33] Right ventricular hypertrophy was stratified as mild, moderate, severe, or unspecified and categorized as concentric, eccentric, or unspecified.[21,33] If the degree of hypertrophy was recorded as a range (mild-moderate), then the more severe stratum (ie. moderate) was selected for the purposes of this study. The subjective degrees of right atrial enlargement and tricuspid valve regurgitation were similarly categorized as mild, moderate, severe, or unspecified. [21,33,34] Right ventricular outflow tract flow profiles were categorized as type I, II, or III.[21,35-38] The presence or absence of abnormal interventricular septal motion was noted and if present, was further classified as paradoxical motion and/or septal flattening.[35-37,40,41] When available, ductal morphology was recorded and designated as type I, II (unrefined), IIa, IIb, or III in accordance with a previously published angiographic classification system.[42] Concurrent cardiovascular co-morbidities including CHD, acquired heart disease, and PFO were noted.

Electrocardiographic diagnosis and the presence or absence of a right axis deviation were recorded when available.[1,43,44] Radiographic reports were reviewed for the presence or absence of cardiomegaly, right heart enlargement, main or peripheral pulmonary artery dilation, focal dilation of the descending aorta (ductal bump), and pulmonary infiltrates.[1,45]

The medical record of each patient was evaluated to determine if specific therapies were employed, including phosphodiesterase-V inhibitors (PDEVi; sildenafil or tadalafil), hydroxyurea, and phlebotomy.[21,24,26,27,29,35,36,46] Total daily PDEVi dose was calculated. Records were also reviewed for adverse treatment reactions. Information regarding any cardiac intervention or surgery was obtained when possible.

Lifetime occurrence of rCHF and survival status were determined for each patient. When survival information was not documented in the medical record, the client and/or referring clinician was contacted.

Statistical Analysis

Statistical analysis was performed using commercially available software (Microsoft Corporation, 2023. *Microsoft Excel for Mac*, available from https://www.microsoft.com/en-us/microsoft-365/excel; SAS 9.4. SAS Institute Ince., Cary, NC). A P-value < 0.05 was deemed significant. Clinical data were arranged in a spreadsheet, and descriptive statistics were performed. Variables were tested for normality using visual inspection of data points and histograms and the Shapiro-Wilk test. Descriptive statistics were reported as mean (+/- standard deviation) for normally

distributed variables and median (range) for nonnormally distributed variables. Categorical variables were reported as proportions and/or percentages.

All cause survival and the potential impact of select variables were interrogated using Kaplan-Meier curves with 95% confidence intervals and log-rank test using the Holm-Sidak pairwise multiple comparisons test when applicable. Specific parameters assessed in this manner included rCHF status, PDEVi therapy, administration of hydroxyurea, therapeutic phlebotomy, PCV, reproductive status, and BCS at initial presentation. PDEVi, hydroxyurea, and therapeutic phlebotomy were investigated as binaries, with patients categorized by whether or not they received the treatment. For analysis of the interaction between PCV and survival, patients were categorized according to initial presenting PCV<65% or ≥65%.[1] Similarly, presenting BCS was stratified as <4, 4-5, or >5. For all-cause death, adjusted hazard ratios (HR) were estimated using multivariate Cox proportional hazard models. Parameters selected for the multivariate analysis included PDEVi, hydroxyurea, therapeutic phlebotomy, presenting PCV, RCF status, age at presentation, BCS at presentation, and reproductive status. HR and 95% confidence intervals (CI) were calculated. Additionally, PDEVi, therapeutic phlebotomy, PCV, rCHF status, and age at presentation were evaluated using a parsimonious model, yielding hazard ratios and 95% CIs. Backward variable selection technique was used to obtain the parsimonious model which included only significant factors.

2.3 Results

Participating institutions were located in the United States (14), United Kingdom (4), and Japan (1). The initial query identified 138 dogs with rPDA. One dog was represented in two independent medical records from different collaborating centers. These data were consolidated, resulting in inclusion of 137 dogs.

Reproductive status was recorded for 136 dogs, with 88 (65%) designated as female and 48 as male (35%). In descending order, represented breeds included mongrel or mixed breed (24), Maltese (13), Chihuahua (10), Yorkshire Terrier (9), Toy Poodle (8), Jack Russel Terrier (7), Dachshund (7), Pomeranian (6); Collie (4), Miniature Dachshund (4), Standard Poodle (4), Welsh Corgi (4); Labrador Retriever (3), Papillon (3); Bernese Mountain Dog (2), Boston Terrier (2), Cocker Spaniel (2), Miniature Poodle (2), Vizsla (2), West Highland White Terrier (2); and one each of Affenpinscher, Alaskan Husky, Australian Cattle Dog, Australian Labradoodle, Australian Shepherd, Bassett Hound, Bichon Frise, Bloodhound, Coton de Tulear, English Springer Spaniel, French Poodle, German Shorthair Pointer, Golden Retriever, Irish Setter, Italian Greyhound, Italian Spinone, Miniature American Eskimo Dog, Miniature Schnauzer, Shetland Sheepdog, and Soft-Coated Wheaton Terrier. Age at presentation was recorded for 136 dogs, with a mean age of 29.1 (+/-27.7) months.

Clinical signs were reported in 128 dogs at initial presentation (93%), and data are summarized in Figure 1. Exercise intolerance was most common (71 dogs, 55%), followed by pelvic limb weakness, differential cyanosis, and syncope, which were described in 54, 48, and 43 dogs, respectively (42%, 38%, and 34%).

The presence or absence of a split S2 sound was specifically documented in 126 dogs, with 59 being positive for the finding (47%). A continuous heart murmur was historically documented at least once in 24 dogs (18%), and a non-continuous or incompletely characterized murmur was recorded at least once in an additional 12 dogs (9%).

Presenting and final BCS were available for 87 and 84 dogs, respectively, and were reported using a scale of one-to-nine. The frequencies of observations for each category are displayed in Tables 1a and 1b. A score of four or five was reported in 65 dogs at initial presentation (75%) and 56 dogs at final evaluation (67%).

Presenting PCV was recorded for 105 dogs, and a total of 41 dogs had a presenting PCV of ≥65% (39%). Maximum PCV was recorded for 108 dogs, with a mean value of 66.6% (+/-12.0).

Echocardiographic and electrocardiographic findings are summarized in Table 2a and Table 2b, respectively, while radiographic findings are represented in Table 3. The electronic medical record of one dog was incomplete due to migration of data to a new system. For this animal, the initial method of diagnosis was not available. Of the remaining 136 dogs, 119 were diagnosed with continuous rPDA based on echocardiography alone (88%), five via a combination of echocardiography and angiography (4%), three by echocardiography and diagnostic catheterization (2%), and one each via the following: echocardiography and nuclear scintigraphy with 99mTc-macroaggregated albumin (<1%); echocardiography, angiography, and diagnostic catheterization (<1%); and echocardiography with computed tomography (<1%). Four dogs were diagnosed with bidirectional PDA shunting via echocardiography and agitated

saline contrast (3%), while two were diagnosed with bidirectional shunting without an agitated saline contrast study (1%). Three dogs within the study population initially exhibited echocardiographic evidence of left-to-right PDA and were subsequently diagnosed with rPDA. In one of these dogs, the inaugural echocardiographic evaluation yielded a maximum trans-ductal spectral Doppler velocity of 4 m/s. Within one month, continuous right-to-left shunting of flow was documented.

Cardiovascular comorbidities were reported in 33 dogs (24%), the most common of which included tricuspid valve dysplasia (11, 8%), ventricular septal defect (6, 4%), and PFO (6, 4%). Data are presented in Table 4. Additionally, dynamic right ventricular outflow tract obstruction was reported in 2 dogs.

The most common cardiac phenotypic features identified sonographically included, abnormal interventricular septal motion (88%), tricuspid valve regurgitation (69%), right atrial enlargement (67%), and right ventricular (RV) concentric hypertrophy (62%). Of the dogs for which a systolic trans-tricuspid pressure gradient was recorded, 58 had a maximum pressure gradient of ≥46.2 mmHg (94%). The mean maximum estimated trans-tricuspid pressure gradient was 95.12 mmHg (+/- 33.2 mmHg).

Electrocardiographic data were available for 85 dogs (Table 2b), of which 59 reportedly had evidence of a right deviation of the mean electrical axis and/or deep S-waves recorded in lead II (69%). Seventy-seven dogs had normal sinus rhythm, sinus tachycardia, or sinus arrhythmia without ectopy (91%). Only one dog was diagnosed with premature ventricular ectopy (1%).

Thoracic radiographs were performed in 90 dogs. The most frequently described abnormalities included cardiomegaly (70, 78%), right chamber enlargement (57, 63%),

and main pulmonary artery enlargement (46, 51%). Aortic root dilation and/or a ‘ductal bump’ was reported in one-third of dogs (30, 33%).

Pharmacotherapy comprised sildenafil for 87 dogs (64%), tadalafil for five (4%), and hydroxyurea for 19 (14%). Specific dosing information for sildenafil was available for 85 of the dogs, and the mean maximum dose was 4.5 mg/kg/day (+/- 2.7). Dosing information for tadalafil was available for all five dogs and the median daily dose was (2.2) mg/kg (2-5 mg/kg). Dosing strategies reported for hydroxyurea were highly variable. Data regarding phlebotomy were available for 126 dogs, and a total of 52 dogs (41%) received this treatment. Two dogs also received a crystalloid fluid parenterally at the time of phlebotomy. Polycythemia was managed via the application of medical leeches in one dog and by parenteral administration of a crystalloid fluid in another dog. Additional cardiac medications included pimobendan (26), enalapril (16), furosemide (12), propranolol (7), aspirin (6), L-arginine (5), spironolactone (3), benazepril (2), hydrocodone (2), beraprost (1), amlodipine (1), atenolol (1), captopril (1), clopidogrel (1), heparin (1), omega-3 fatty acid supplement (1), pentoxifylline (1), sotalol (1), theophylline (1), an unspecified angiotensin converting enzyme inhibitor (1), and an unspecified diuretic (1).

Adverse reactions to phlebotomy and pharmacotherapy were reported in two and 12 dogs, respectively. Half of the recorded medication-related side effects involved various blood dyscrasias in patients receiving hydroxyurea. In the dog managed with medical leeches, an excessive decline in PCV was observed following one treatment session, and in another dog, PCV initially increased immediately after phlebotomy. The adverse drug reactions included: intermittent emesis associated with excitement in one

dog receiving pimobendan, hydroxyurea, and sildenafil; alopecia in one dog treated with hydroxyurea, sildenafil, and beraprost; and diarrhea, trembling, and paraphimosis were observed in one dog each during administration of sildenafil.

The following hematologic abnormalities were documented in dogs receiving hydroxyurea: a combination of thrombocytopenia and neutropenia in two dogs (11%), leukopenia in two dogs (11%), monocytopenia in one dog (2%), and isolated neutropenia in one dog (2%). The dog that developed monocytopenia also exhibited thrombocytopenia prior to initiation of hydroxyurea.

PDA closure was attempted in 4 dogs. Specifically, trans-catheter placement of a vascular occlusion device was successfully performed in 3 dogs subsequent to implementing PDEVi therapy. These animals were initially diagnosed with rPDA, though following sildenafil administration, left-to-right ductal flow was restored. Sildenafil was eventually discontinued in all 3 dogs. Surgical ligation was attempted in one dog with bi-directional PDA shunting. A PDEVi was not instituted prior to surgery, and the patient was euthanized within 24 hours of the procedure due to lack of clinical improvement.

Overall median survival time (MST; 95% CI, first quantile-third quantile) was 88.0 months (73.8-98.4, 32.5-121.9) (Figure 2). Bivariate analysis for all-cause survival identified PDEVi administration, treatment with hydroxyurea, and therapeutic phlebotomy as factors that were associated with a statistically significant increase in MST. Resulting Kaplan-Meier curves are depicted in Figure 3. The MST was 90.6 months (74.4-121.9, 71.5-123.1) for dogs that received a PDEVi versus 18.6 months (5.8-88.0, 7.0-98.0) for those that did not ($p= 0.008$); 123.1 months (87.8-132.5, 87.8-132.5) for those that received hydroxyurea versus 73.9 months (40.0-90.2, 31.9-98.0) for those

that did not (p= 0.008); and 112.4 months (74.4-129.1, 73.8-131.0) for those that were treated with therapeutic phlebotomy versus 83.8 (36.9-90.2, 23.9-90.2) for those that were not (p< 0.001). Sex, defined as a male versus female binary, was not associated with a statistically significant difference in MST (p= 0.74). However, sex was also analyzed as a function of reproductive status, yielding four distinct categories. These differentiated reproductively intact and reproductively altered individuals within each sex. The MST was greater for reproductively altered males (109.9 months; 90.64-greater than maximum survival, 90.6-129.1; p=0.009) and females (94.8 months; 74.4-145.2, 88.0-145.2; p=0.002) as compared to reproductively intact females (51.0 months; 11.87-87.8, 8.1-98.0). Neither rCHF status (0.052), PCV≥65% (p=0.397), nor presenting BCS (p=0.113) were associated with statistically significant differences in MST.

Reproductive status was not associated with survival in the multivariate analysis (p>0.7412). There was, however, a statistically significant correlation between survival and age at presentation (p<0.001), with the risk of death decreasing by 3% for every additional month of age (HR 0.97, 0.96-0.99). As determined by the full multivariate model, the only factors associated with a statistically significant reduction in all-cause survival were a PCV≥65% (HR 3.80, 1.47-9.79; p=0.006) and the absence of therapeutic phlebotomy (HR 3.13, 1.25-7.80; p=0.014).

Age at presentation (p<0.001), PCV≥65% (p=0.005), PDEVi status (p=0.016), therapeutic phlebotomy (p<0.001), and rCHF status (p=0.047) were identified as significantly associated with survival in the parsimonious model. Dogs with PCV≥65% and those that were not treated with either phlebotomy or a PDEVi experienced a reduction in all-cause survival. Conversely, all-cause survival was increased in dogs that

were older at initial presentation and those that did not develop rCHF. Corresponding HRs are presented in Table 5.

2.4 Discussion

Canine rPDA is an uncommon clinical phenomenon that is, nevertheless, a source of significant morbidity and mortality in affected dogs.[1,29] Inherent to the etiopathogenesis of the condition is the perpetuation or development of suprasystemic pulmonary vascular pressures.[1,6,11,14,19] This severe PH, in conjunction with the hypoxemic sequala of right-to-left shunting, dictates the clinical signs, physical examination findings, hematologic consequences, and cardiac phenotype that define rPDA. The objective of this retrospective, multi-center study was to describe these features in a large, geographically diverse population of dogs.

Patent ductus arteriosus preferentially affects small-breed, female dogs.[1,3-5,7] As this form of CHD represents the anatomical substrate for rPDA, it is unsurprising that a preponderance of dogs included in the present study were female. Further, dog breeds previously reported to be predisposed to PDA, such as Chihuahua, Maltese, Yorkshire Terrier, and Toy Poodle, were among the most common represented in our population.[1,3,7] The mean age at diagnosis was relatively young at approximately 2.4 years. However, as rPDA is a form of cyanotic CHD, an even earlier age of presentation might be anticipated. The apparent delay may, in part, be attributable to the comparatively cryptic physical examination findings that are reported in dogs with rPDA.[1,6,24,47] Salient abnormalities may elude even an astute clinician unless a client reports clinical signs that sufficiently raise the index of suspicion for CHD. For example, differential cyanosis may not be apparent without provocative testing (exercise or exertion in the clinical setting).[1,13] The majority of dogs in the present study did not have a heart murmur at the time of diagnosis, thus eliminating a finding that might readily alert

a clinician to latent CHD.[47-49] A split S2 sound, which can signify severe pulmonary hypertension, was common. However, this abnormality can be subtle and may be challenging to identify in the primary care setting.[6,24,49] It must also be recognized that a split S2 is far from pathognomonic for rPDA and has been reported in association with a variety of congenital heart anomalies, most notably atrial septal defects[1,49].

The etiopathogenesis of right-to left shunting may also partially explain the mean age of diagnosis in dogs with rPDA. By virtue of pulmonary over-circulation and increased endothelial shear stress, there is a recognized association between left-to-right congenital cardiac shunts and PH.[7,15,18,20,21] Vasoconstriction and chronic vascular remodeling are promoted by dysfunction of the nitric oxide, thromboxane, prostacyclin, and endothelin signaling pathways, among others.[13,15] Inflammation, medial hypertrophy, and intimal proliferation collectively increase pulmonary vascular resistance, the latter being the defining feature of pre-capillary PH.[13,18,21] This scenario is distinct from post-capillary pulmonary hypertension, in which increased pulmonary artery pressure is a corollary of elevated left atrial pressure. However, both phenomena can occur concomitantly in patients with uncorrected left-to-right cardiac shunts.[18,21,36] Severe PH is evidenced histologically by the presence of plexiform lesions. These vascular abnormalities are the irreversible hallmark of World Health Organization Group 1 pulmonary hypertension, which includes PH associated with congenital cardiac shunts.[20,50] The ACVIM Consensus statement pertaining to canine pulmonary hypertension similarly identifies PH associated with congenital cardiac shunts as a subcategory of Group 1 PH (Group 1d1).[21] Eisenmenger's syndrome is the most advanced clinical manifestation of PH in patients belonging to Group 1d1, and its

characteristic attribute is shunt reversal due to suprasystemic pulmonary vascular resistance.[13-15]

Patients with an anatomical shunt, such as PDA, may also exhibit right-to-left shunting if pulmonary vascular resistance remains inordinately high following birth.[11,19] In humans, this phenomenon is termed persistent pulmonary hypertension of the newborn (formerly persistent fetal circulation), and it may be a consequence of pulmonary vasoconstriction, vascular remodeling, or both. Persistent pulmonary hypertension of the newborn can occur as an idiopathic process, accounting for 10-20% of all cases.[19] Myriad secondary causes have also been recognized and include meconium aspiration syndrome, pneumonia, alveolar capillary dysplasia, associated congenital heart disease, and conditions featuring lung hypoplasia or hypoplastic pulmonary vasculature.[11,19] Children affected by severe persistent pulmonary hypertension of the newborn can experience intrapulmonary and extrapulmonary right-to-left shunting (via a PFO or PDA), both of which contribute to hypoxemia. Historically, the ES model has been considered the most probable explanation for severe PH in dogs with rPDA.[6,7] While this remains the dominant paradigm, it seems probable that some dogs manifest rPDA due to persistent post-natal PH.

The most frequently reported clinical signs in dogs with rPDA are readily referrable to severe pulmonary hypertension, caudal hypoxemia, and/or secondary polycythemia.[1,21] Exercise intolerance was most common in the current study, followed by hind limb weakness or loss of postural tone, differential cyanosis, and syncope. RCHF and neurologic signs were reported in a minority of dogs and likely represent late-stage manifestations of severe PH and hyperviscosity syndrome, respectively.[1] In the recent

retrospective evaluation of 43 client-owned dogs with rPDA conducted by Greet et al, the majority of animals presented with clinical signs. In contrast to our data, the investigators determined that hind limb collapse was most common, followed by exercise intolerance.[29] That study also indicated that rCHF and neurologic signs were uncommon, mirroring the findings of our investigation.

Previous studies have demonstrated that cachexia is associated with decreased median survival time in companion animals with congestive heart failure.[31,51,52] Some of these investigations have determined that survival is correlated with muscle condition score (MCS) but not BCS, while others have indicated that survival time declines in patients with low BCS when compared to patients with increased BCS. Further, a study evaluating the MCS for assessment of muscle mass in dogs noted that BCS correlated with MCS. However, the investigators cautioned that the two parameters are not directly related.[30] Overall, these studies indicate that MCS is the superior metric for identifying cachexia in companion animals with congestive heart failure.[31,51,52] In the present retrospective analysis, electronic medical records from the primary institution and several collaborating centers commonly recorded BCS but not MCS. Hence the former was examined for overall population trends. At both presentation and final evaluation, the majority of dogs had a normal BCS (4-5).[30,31] Changes in BCS for individual dogs were not analyzed over time.

Echocardiography, typically with the aid of an agitated saline contrast study, has previously been reported to be an effective means of diagnosing rPDA in dogs.[1,24,26,29] This was the most commonly employed imaging modality in the present study, though advanced imaging and cardiac catheterization were also reported. During

echocardiography, the complete rPDA cannot be visualized directly. Thus, clinical context, echocardiographic signs of severe PH, and opacification of the descending aorta, but not the left cardiac chambers, with agitated saline allow the clinician to infer the presence of a pulmonary-to-aortic shunt. One dog in this study was diagnosed via nuclear scintigraphy and 99mTc-macroaggregated albumin, a method that has previously been described for the identification of right-to-left congenital cardiac shunts.[53-54] The most common echocardiographic findings in our study have previously been identified as signifiers of pulmonary hypertension and included RV concentric hypertrophy, RA enlargement, abnormal interventricular septal motion, tricuspid valve regurgitation, normal to decreased left cardiac chamber dimensions, and an estimated maximum trans-tricuspid pressure gradient ≥46.2 mmHg (corresponding to a velocity of ≥3.4 m/s).[1,21,36,37] The lattermost finding was present in 94% of dogs for which tricuspid valve velocity was recorded. Additionally, the mean maximum trans-tricuspid pressure gradient was approximately 95 mmHg, which has traditionally been considered to be reliable estimate of a severe elevation of pulmonary artery pressures.[36]

The morphology of the PDA was recorded using the Miller angiographic classification system in a minority of dogs.[42] In this study, the morphology was visualized via transthoracic echocardiography, though various imaging modalities are not interchangeable for assessment of PDA size and geometry.[55] The ductal morphology was recorded as type II (abrupt distal tapering of >50%) in six dogs and type III (tubular) in three dogs. Previously, it has been reported that dogs with ES and rPDA tend to have a large diameter PDA.[1,6,7] Large shunt diameter is also recognized as a contributing factor in human ES.[14,17,50] Consequently, the minimal ductal flow orifice may be of greater

significance in predicting the development of ES than angiographic morphology. When evaluated via 3D transesophageal echocardiography, the pulmonary ostium of a canine PDA may be ovular in shape.[55] Thus, minimal ductal diameter can be underestimated by transthoracic echocardiography, depending on the plane of imaging.

In our cohort of dogs, the most common radiographic findings were as expected for patients with PDA and PH.[1,45] Cardiomegaly, right chamber enlargement, and expansion of the main pulmonary artery were identified in a majority of animals. Additionally, aortic root enlargement or a 'ductal bump' was noted in approximately one-third of dogs, while peripheral pulmonary artery enlargement was documented in one-fifth. This data may aid in identifying patients with possible rPDA prior to referral for echocardiography. For example, a primary care clinician's degree of suspicion for rPDA may be augmented if thoracic radiography discloses cardiomegaly, pulmonary artery dilation, and aortic root enlargement in a young, polycythemic dog.

Electrocardiographic examinations yielded findings suggestive of right ventricular chamber enlargement.[43,44] It was not feasible to determine the mean electrical axis of ventricular depolarization in all patients that received an electrocardiographic evaluation, as often only lead II was evaluated. However, the presence of deep-S waves in lead II evinces a deviation of the mean electrical axis. Given concomitant echocardiographic findings in this population, a right-axis shift due to RV hypertrophy was considered most likely.[1,43] Right bundle branch block also instigates a right deviation of the mean electrical axis but simultaneously increases the QRS duration.[44] Similarly, deep S-waves may be observed in lead II recordings of patients with isolated left anterior fascicular block. Thus, a 6- or 10-lead ECG recording could be used to screen dogs with suspected

rPDA for corroborating evidence of right chamber enlargement prior to referral. In humans with ES, the prevalence of organized atrial tachycardia is 15-20%, while that of non-sustained ventricular tachycardia is five-ten%.[14] This is incongruous with the findings of the current study, in which only two dogs had premature atrial ectopy and one dog had premature ventricular ectopy based on available ECG data. However, Ambulatory ECG monitoring was not performed, and the prevalence of arrhythmias in these dogs may be underestimated.

Chronic hypoxia is a cardinal feature of ES and provokes secondary polycythemia. In response to reduced oxygen delivery, the kidneys increase production of erythropoietin, thereby attempting to generate a compensatory expansion of oxygen carrying capacity.[14,56] However, the resultant increase in PCV can become maladaptive, leading to hyperviscosity syndrome and increased risk of thrombosis.[1,14] Classically, phlebotomy has been considered a fundamental strategy for managing patients with ES.[1,24] This treatment may be performed when the PCV exceeds 65% but is typically only advocated when dogs are exhibiting corresponding clinical signs. The purpose of this judicious approach is to limit fluctuations in blood volume and oxygen carrying capacity. In humans affected by ES, anemia and iron depletion imposed by serial phlebotomy are a significant concern.[14] Consequently, routine phlebotomy is no longer recommended. When it is deemed necessary, it is performed in concert with parenteral fluid administration to avoid hemodynamic alterations. Approximately 41% of the dogs in the current study had at least one episode of therapeutic phlebotomy, and only two received a parenteral crystalloid concomitantly. Minor adverse reactions were noted in two dogs following phlebotomy. In one of these animals, the use of medical leeches

resulted in a greater than intended decline in PCV. This may highlight the relatively imprecise control of erythrocytosis that can be achieved via leech application. With conventional methods, it is recommended that an equation be used to calculate the target volume for extraction.[24] Again, the majority of dogs that received phlebotomy in the current study reportedly tolerated this treatment well.

Pharmacotherapeutic regimens have also been described for management of polycythemia in dogs with ES. Chronic hydroxyurea provided a viable alternative to phlebotomy in a case series of 4 dogs with rPDA.[26] Hydroxyurea is an antineoplastic DNA synthesis inhibitor that has been used to address polycythemia in companion animals. Adverse effects include cytopenias, vomiting, anorexia, and alopecia. A small number of dogs in the current study were treated with hydroxyurea, and a minority developed blood dyscrasias. Following initial evaluation, many of the dogs received ongoing treatment and diagnostic monitoring via one or more primary care veterinarians. Accordingly, there was not reliable access to documents for all lifetime occurrences of phlebotomy. Our data, therefore, did not allow us to confidently assess any changes in the frequency of phlebotomy subsequent to initiation of hydroxyurea.

A separate case series described the effects of sildenafil therapy in 5 dogs with ES.[27] The PCV of all dogs decreased significantly relative to baseline following 3 months of treatment, and each dog achieved a PCV of <65%. No significant adverse effects were observed. Sildenafil is a PDEVi that has been employed for management of pulmonary hypertension in dogs.[35,36,57,58] By antagonizing the action of phosphodiesterase V, sildenafil yields increased levels of cyclic guanylate monophosphate within vascular smooth muscle.[21,35,50] This augments the capacity for endogenous nitric oxide, which

activates cyclic guanylate monophosphate, to effect pulmonary arterial vasodilation. Previous studies investigating the efficacy of sildenafil in dogs with pulmonary hypertension have reported improvement in clinical status and quality of life.[35,58] In a recent prospective study involving dogs with pulmonary hypertension, tadalafil, another PDEVi, yielded improvements in quality of life scores that were comparable to those achieved with sildenafil.[46] Tadalafil also afforded the added benefit of once-daily dosing. The ACVIM consensus statement on canine pulmonary hypertension advocates the use of PDEVi therapy in dogs with Group 1a, 1b, and 1c PH, while also noting that it may be considered for clinical management of dogs with Group 1d1 PH.[21] Approximately 67% of dogs in the present descriptive study were treated with a PDEVi, and adverse effects were rarely reported.

In human patients with ES, PDEVi medications are recommended as a first-line therapy for mitigation of PH.[14] Alternatively, endothelin-1 antagonists can be implemented for initial monotherapy, and prostacyclins can be added for multi-modal treatment. The current ACVIM consensus statement on canine pulmonary hypertension does not advocate for the use of endothelin-1 antagonists or prostanoids in dogs, as there is a paucity of data in the veterinary literature concerning their safety and efficacy.[21] Further, these agents tend to be cost-prohibitive and/or require methods of administration that may be impractical.[36] One dog in our study population received beraprost for management of PH. This is an oral prostacyclin analog that exerts a robust vasodilatory effect on pulmonary arteries.[36,59] Randomized trials have investigated the efficacy of beraprost in humans with PH, and patients with idiopathic PH demonstrated improved exercise tolerance following three months of treatment.[59,60] However, this benefit was not

conferred to patients with ES. Recently, beraprost has been shown to be effective in a small cohort of dogs diagnosed with PS when administered at approximate doses of 15 ug/kg twice daily.[61]

Conventional wisdom dictates that ductal closure is contraindicated in patients with ES and unidirectional right-to-left shunting.[21,50,62] Such intervention may dramatically increase right ventricular afterload, resulting in greater morbidity and mortality.[1] Previous studies and case reports have, however, chronicled the feasibility of PDA closure in companion animals with PH and persistent left-to-right flow.[29,57,63,64] Often, the patients in these studies were treated with sildenafil prior to or at the time of shunt closure. In some reports, invasive right ventricular pressure monitoring was conducted at the time of intervention to assess patient response before definitive closure.[62,63] A recent human report explored the feasibility of trans-catheter ductal closure in patients with PDA and ES.[61] Definitive closure was performed in four patients following 12 months of targeted PH therapies comprising various endothelin receptor antagonists and PDEVi medications. A significant reduction in pulmonary artery systolic pressure was observed in all four patients immediately after closure. In the recent retrospective study involving 43 dogs and three cats with reversed or bi-directional PDA, closure was attempted in six animals.[29] Five of six received sildenafil, and all six demonstrated bi-directional shunting prior to closure. Three animals died during or immediately after the procedure, while the remaining three experienced a good long-term outcome. Ductal closure was performed in four dogs included in the present study population. Three of the four received sildenafil prior to intervention, yielding continuous

left-to-right flow. Trans-catheter occlusion was performed successfully in all three dogs. Subsequently, these patients tolerated discontinuation of sildenafil. The remaining dog did not receive sildenafil prior to surgical ligation and was euthanized in the immediate post-operative period. Though limited, these data suggest that PDA closure may be feasible in dogs with rPDA if continuous left-to-right shunting is documented following initiation of a PDEVi. Hemodynamic monitoring during the procedure, but prior to definitive closure, may also aid in identifying patients most likely to benefit. Further study is required to determine the safety and efficacy of combined targeted PH therapy and PDA closure in patients with rPDA.

Median survival time for our study population indicates that dogs with rPDA commonly live to maturity but typically do not reach geriatric age. In bivariate analysis, PDEVi therapy, hydroxyurea, and phlebotomy were significantly correlated with increased survival. Further the most striking disparity in median survival between dogs that received a particular treatment and those that did not was observed in the examination of PDEVi treatment.

Hydroxyurea and PDEVi administration were independently associated with increased survival time in the parsimonious multivariate analysis. Greet et al also demonstrated a correlation between survival and PDEVi therapy. Given the retrospective nature of both studies, any conclusions regarding the efficacy of a specific treatment are somewhat dubious. Our investigation was not designed to assess alterations in quality of life with respect to specific treatment modalities. However, there is relatively robust evidence in the veterinary literature to demonstrate improved quality of life in dogs that receive sildenafil for amelioration of PH. Additionally, there are limited data to suggest

that hydroxyurea and PDEVi medications maintain a PCV of <65%. Consequently, improvement in owner-perceived quality of life and the mitigation of polycythemia might contribute to a delay in death or euthanasia for dogs that receive these treatments. Ideally, prospective studies pertaining to survival and owner-perceived quality of life would be conducted in the future to elucidate the efficacy of various treatments. However, the rarity of rPDA will likely pose a challenge for patient enrollment.

The BCS was evaluated to determine if a presenting score <4 or >5 was associated with a difference in median survival, though findings did not reach statistical significance. This may reflect the lack of direct relationship between BCS and MCS, with the latter representing a better index of cachexia.[30,51,52]

Surprisingly, the survival difference between dogs that developed rCHF and those that did not approached, but did not reach, statistical significance in the univariate model. This was counter to our expectations and also to the findings of Greet et al. The retrospective study by the latter demonstrated that survival time was reduced for dogs with rCHF. This disparity may be explained by methodology, as our study evaluated dogs with a lifetime occurrence of rCHF, and the previous investigation examined dogs with rCHF at initial presentation. However, the lack of rCHF was independently associated with improved survival when our patient population was evaluated using the parsimonious model. In humans with ES, rCHF is also associated with a poor prognosis and is an indication for lung or heart and lung transplantation.[50]

Median survival time for reproductively intact females was decreased relative to altered males and females. This likely reflects severity of disease in the intact females, as the risks associated with general anesthesia may have precluded ovariohysterectomy.

Further, females were over-represented in the study, and orchiectomy typically requires a shorter duration of general anesthesia than ovariohysterectomy. Both of these factors may account for the lack of statistically different survival between intact males and reproductively altered dogs.

In the multivariate analysis, reproductive status was not associated with a statistically significant difference in survival, though age at presentation was. This was true in the complete multivariate analysis, as well as the parsimonious model. The investigators conjecture that, for the reasons detailed previously, dogs with mild clinical signs secondary to rPDA may be challenging to identify early in life. A more comprehensive evaluation for cardiovascular disease may, therefor, not be pursued until PH becomes more advanced and clinical signs are more pronounced. Conversely, dogs in which manifestations of severe PH are appreciated at a young age are likely to be diagnosed with rPDA earlier. Due to the severity of the underlying disease, these patients may also experience reduced survival.

A presenting PCV of ≥65% and a lack of therapeutic phlebotomy were also associated with decreased survival in the comprehensive and parsimonious multivariate analyses. Again, the physiologic effects of polycythemia and owner-perceived quality of life may affect time to death or euthanasia in patients with rPDA. However, further investigation in this area is required.

The current study had a number of limitations. The retrospective nature of the investigation limited the parameters that could be quantified or qualified. Additionally, it precluded the ability to draw conclusions regarding any causal relationship between various treatment modalities and survival. The aggregation of data from multiple centers

increased the number of dogs with rPDA available for inclusion. However, it also introduced a great deal of heterogeneity with respect to methods of diagnostic evaluation, image acquisition and measurement, stratification of parameter severity, and management. A contrast study was not performed in all dogs, and consequently, some animals were diagnosed with rPDA based on polycythemia, compatible clinical signs, and echocardiographic indicators of severe PH. Further, many dogs were diagnosed based on the aforementioned factors and the results of an agitated saline contrast study. As angiographic imaging was not performed in these animals, a different form of pulmonary-to-systemic shunt could not be definitively excluded. Often, comprehensive medical records were not available for individual patients, as chronic care and monitoring were performed by the dog's primary veterinarian. This limited our ability to assess temporal trends in clinical parameters, such as BCS or PCV. It also contributed to a lack of precise detail regarding the cause of patient death. For this reason, we elected to assess all-cause mortality rather than cardiac versus non-cardiac causes of death. The duration of the study period undoubtedly influenced the relative number of dogs receiving PDEVi therapy versus phlebotomy. Because the study period began in 1980, some dogs were managed in an era when PDEVi medications were not available. This may have introduced bias into the survival analysis. We did not perform subanalysis of survival based on whether a patient was diagnosed before or after sildenafil was patented. Finally, the etiology of severe PH was often presumptive and based on the presence of a congenital shunt. Patients were not systematically evaluated for evidence of persistent pulmonary hypertension of the newborn or other causes of PH (non-Group 1d1 PH).[21]

To date, this represents the largest retrospective descriptive study detailing the clinical features of canine rPDA. Clinical signs, physical examination abnormalities, and diagnostic findings were as expected for patients experiencing a combination of severe PH, chronic hypoxia, and polycythemia. RCHF was rare. Previously reported treatment modalities including phlebotomy, hydroxyurea, and sildenafil were associated with improved survival in our population of dogs. Finally, ductal closure was attempted in a minority of dogs. The intervention was successful in those that reverted to left-to-right ductal shunting after beginning PDEVi therapy.

Chapter 3

CONCLUSIONS AND AREAS FOR FUTURE EXPLORATION

Reversed patent ductus arteriosus (rPDA) is a rare clinical entity in dogs. Consequently, the majority of the salient veterinary literature comprises anecdotal reports and small case series. Yet, this condition exerts significant morbidity and mortality in affected dogs, illuminating the need for a more comprehensive description of the clinical features and natural history of rPDA. Recently, a retrospective study was published detailing the disease in 43 dogs from the United Kingdom.[1] However, the research described in Chapter 2 represents the largest retrospective effort to date to describe crucial clinical facets of canine rPDA. Moreover, the study population included dogs from geographically diverse regions.

Unless dogs are exhibiting overt signs of severe pulmonary arterial hypertension (PH) or hyperviscosity syndrome, it may be challenging to identify patients with rPDA in the primary care setting. If an owner perceives a blunting of exercise capacity but no abnormal cardiopulmonary sounds are detected during thoracic auscultation, the evaluation may not immediately escalate to referral for echocardiography. Further, classic findings, such as differential cyanosis, may only manifest during exertion. This scenario represents a diagnostic challenge that could delay patient care. Thus a thorough description of the common physical examination, hematologic, electrocardiographic, and radiographic perturbations observed in dogs with rPDA may empower primary care veterinarians to identify potentially affected animals earlier. By extension, this could result in more expedient referral and treatment. For example, if an astute veterinarian notes that a young adult dog with sporadic episodes of hindlimb weakness also has a

mildly increased packed cell volume (PCV), they might perform radiography and electrocardiography in the primary care setting. Cardiomegaly with an aortic 'ductal bump' and a concurrent right deviation in the mean electrical axis would substantially increase the index of suspicion for rPDA based on the observations of the present study.

Clinical management of rPDA comprises therapies that have been reported to ameliorate polycythemia and/or PH. As described in Chapter 2, A parsimonious multivariate model identified phlebotomy, phosphodiesterase-V inhibitor (PDEVi) medications, and hydroxyurea as treatments that were associated with improved survival. Further, adverse effects were rarely reported. Interestingly, phlebotomy is no longer recommended for routine management of human patients with Eisenmenger's syndrome (ES).[2] Instead, targeted therapy for PH represents first-line treatment, and a multi-modal approach is applied in patients with refractory or progressive clinical symptoms.[2,3] Pharmacotherapeutics include PDEVi, endothelin receptor antagonists, and prostacyclin analogs.[4] Patients that continue to deteriorate may undergo lung or heart and lung transplantation.

Currently, there is no published evidence to indicate that a particular therapy is superior to others for the management of canine rPDA. Many of the targeted PH treatments employed in humans are either limited by the route and frequency of administration or are currently cost-prohibitive.[4] Phosphodiesterase-V inhibitors such as sildenafil and tadalafil, however, are readily accessible and appear promising. Previous studies have indicated that this medication improves quality of life in dogs with pulmonary hypertension, and a retrospective analysis indicated that survival was greater in rPDA dogs that were treated with sildenafil.[1,5,6] Beyond the potential impact on survival,

sildenafil may also confer control of polycythemia without the adverse effect profile of hydroxyurea. Ideally, prospective studies pertaining to survival and owner-perceived quality of life would be conducted in the future. This research would have the potential to elucidate the efficacy and comparative superiority of various treatments. However, the rarity of rPDA will likely pose a challenge for patient enrollment.

As discussed in Chapter 2, a minority of dogs with rPDA revert to systemic-to-pulmonary shunting after beginning a PDEVi. This may allow closure of the patent ductus arteriosus (PDA), though it is currently unclear whether such intervention yields a substantive improvement in survival. Invasive hemodynamic monitoring seems to be a prudent means of verifying that an individual dog will tolerate definitive ductal closure.[7,8] Further reports regarding safety and efficacy are required. Additionally, a systematic evaluation of patients for which shunt closure is feasible might elucidate individual factors correlated with success.

The retrospective nature of our study limited our ability to assess the efficacy of various treatments. With respect to survival, the design permitted evaluation of associations but not causation. Similarly, it was not possible to compare the efficacy of different therapies. Finally, the study was not designed to examine the impact of treatments on owner-perceived quality of life.

This thesis provides descriptive data that detail the clinical manifestations of rPDA in dogs. The findings may aid in the identification of dogs with this relatively uncommon form of congenital heart disease, creating the opportunity for medical therapy. Treatment with PDEVi medications, phlebotomy, and hydroxyurea were all associated with increased survival.

APPENDIX 1: FIGURES

Figure 1. Histograms indicate the absolute number of dogs exhibiting sundry clinical signs at the time of initial presentation. Categories are not mutually exclusive.

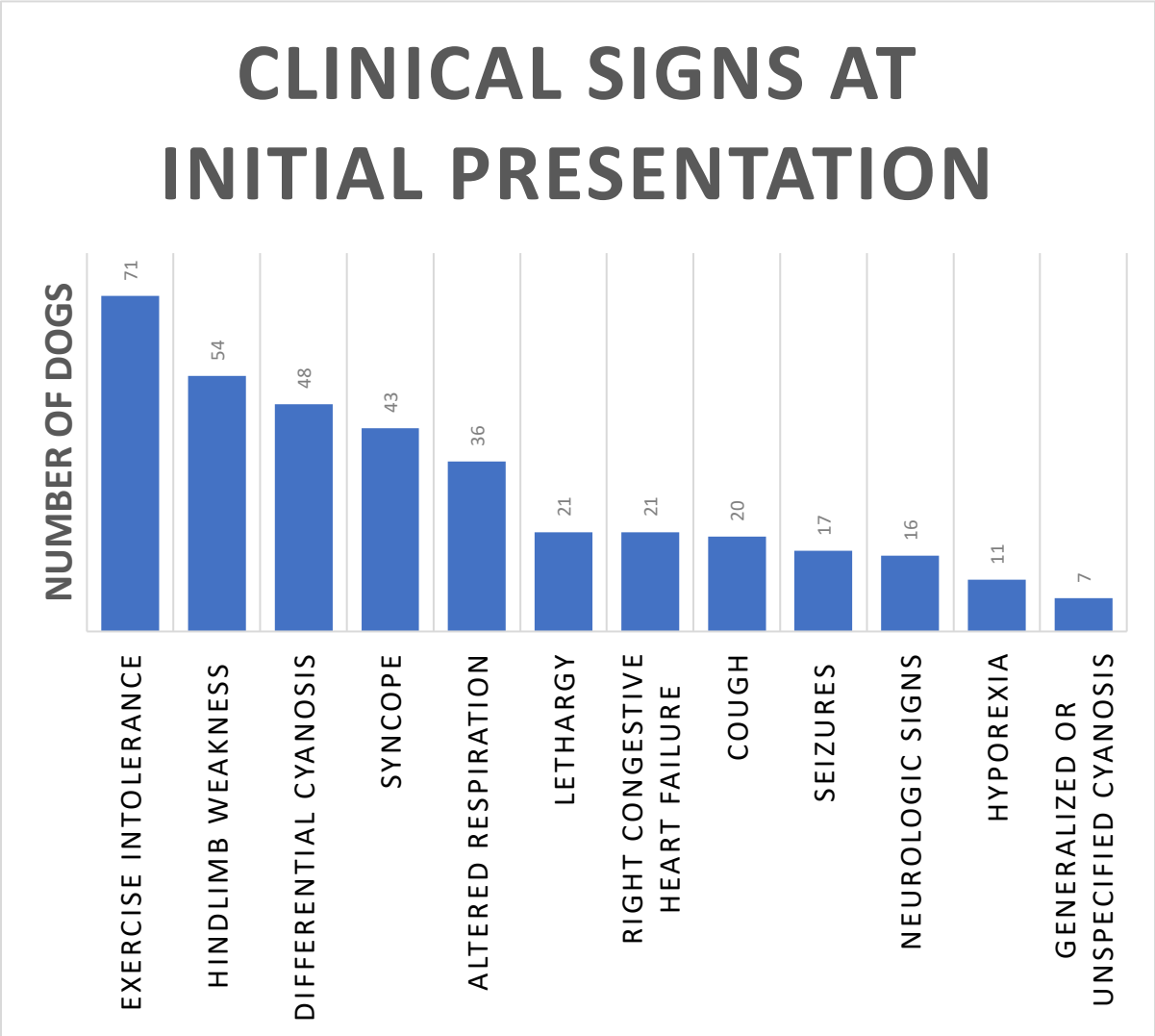


Figure 2. Kaplan-Meier curve depicting overall survival of dogs with reverse patent ductus arteriosus. The area of blue shading represents the 95% Hall-Wellner Band.

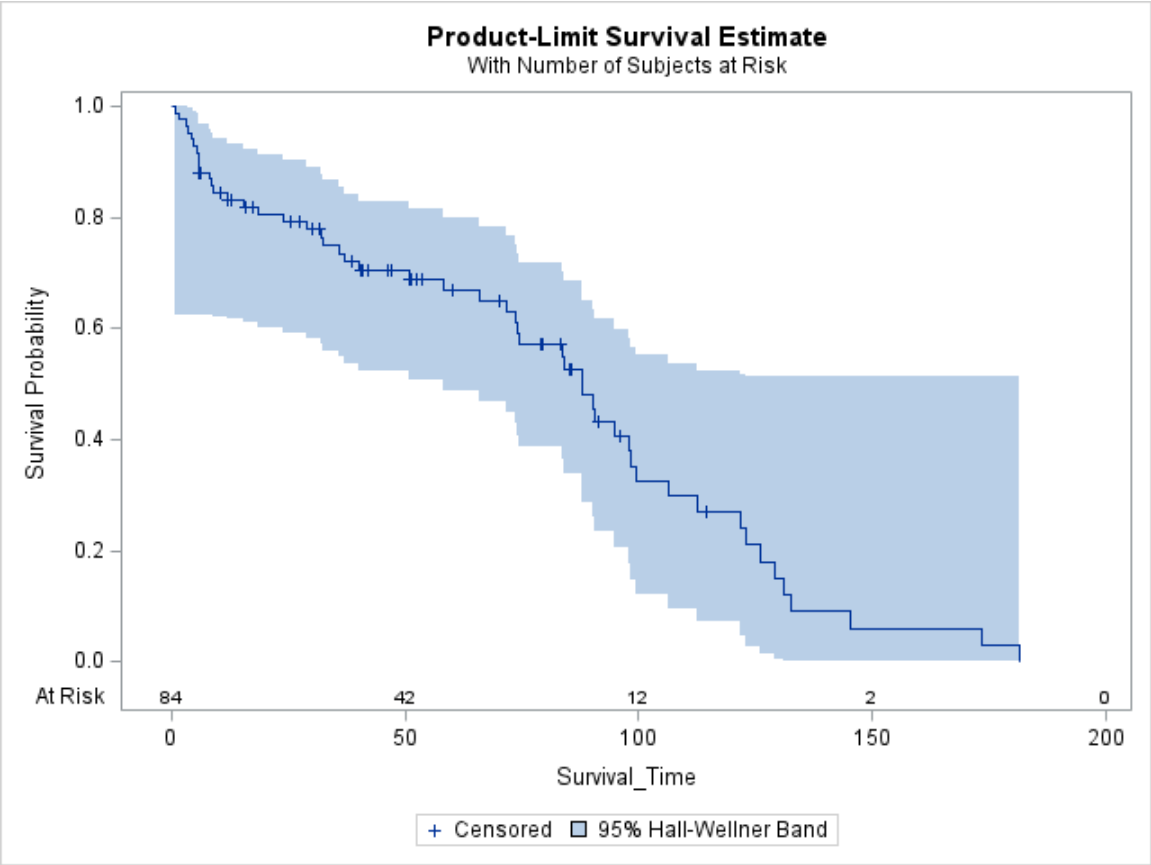


Figure 3a. Kaplan-Meier curve depicting differences in survival between dogs with reverse patent ductus arteriosus that received a phosphodiesterase V (PDEV) inhibitor and those that did not.

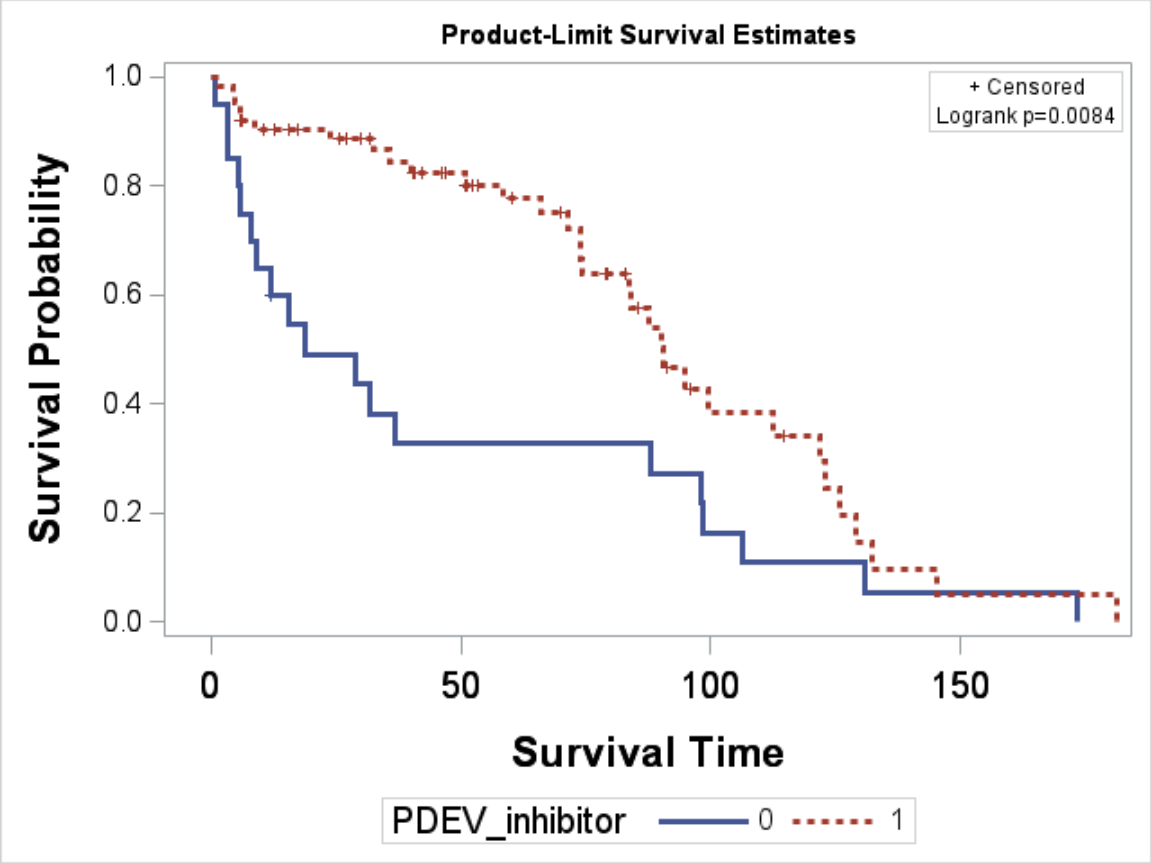


Figure 3b. Kaplan-Meier curve depicting differences in survival between dogs with reverse patent ductus arteriosus that received hydroxyurea and those that did not.

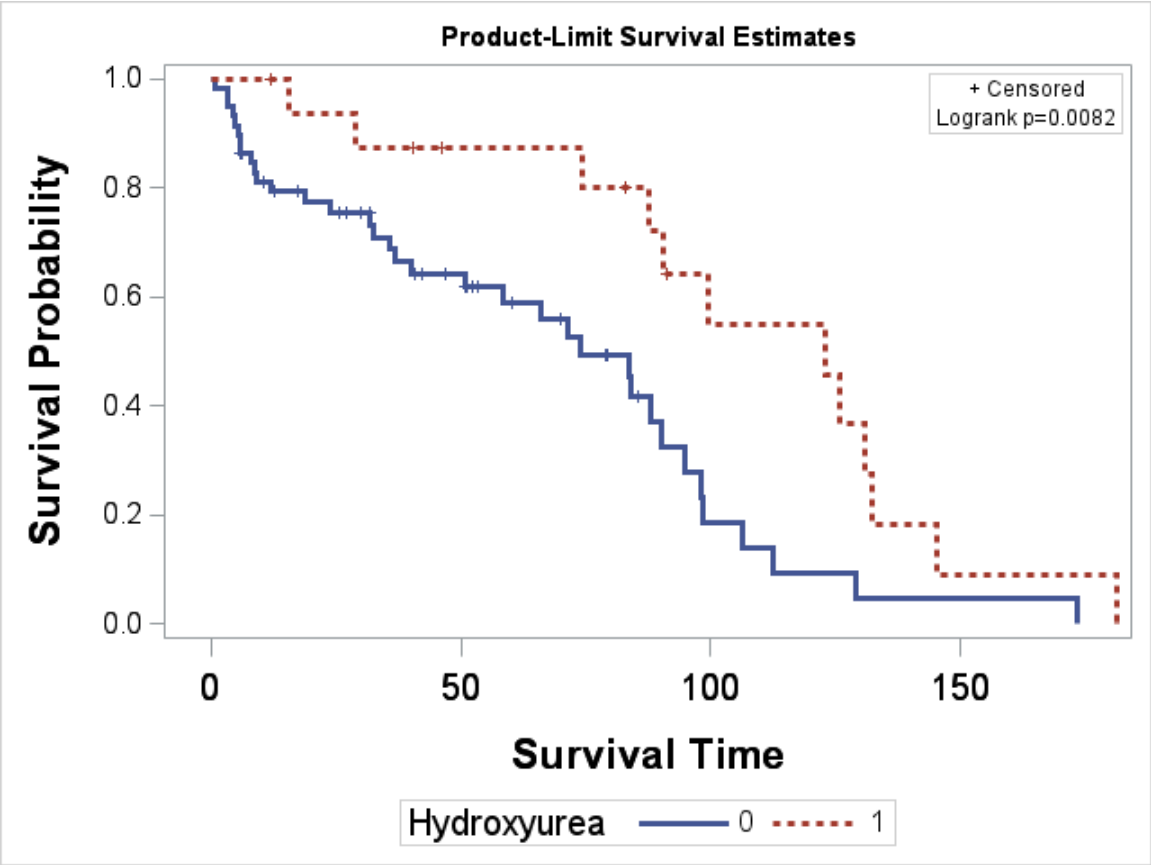


Figure 3c. Kaplan-Meier curve depicting differences in survival between dogs with reverse patent ductus arteriosus that received therapeutic phlebotomy and those that did not.

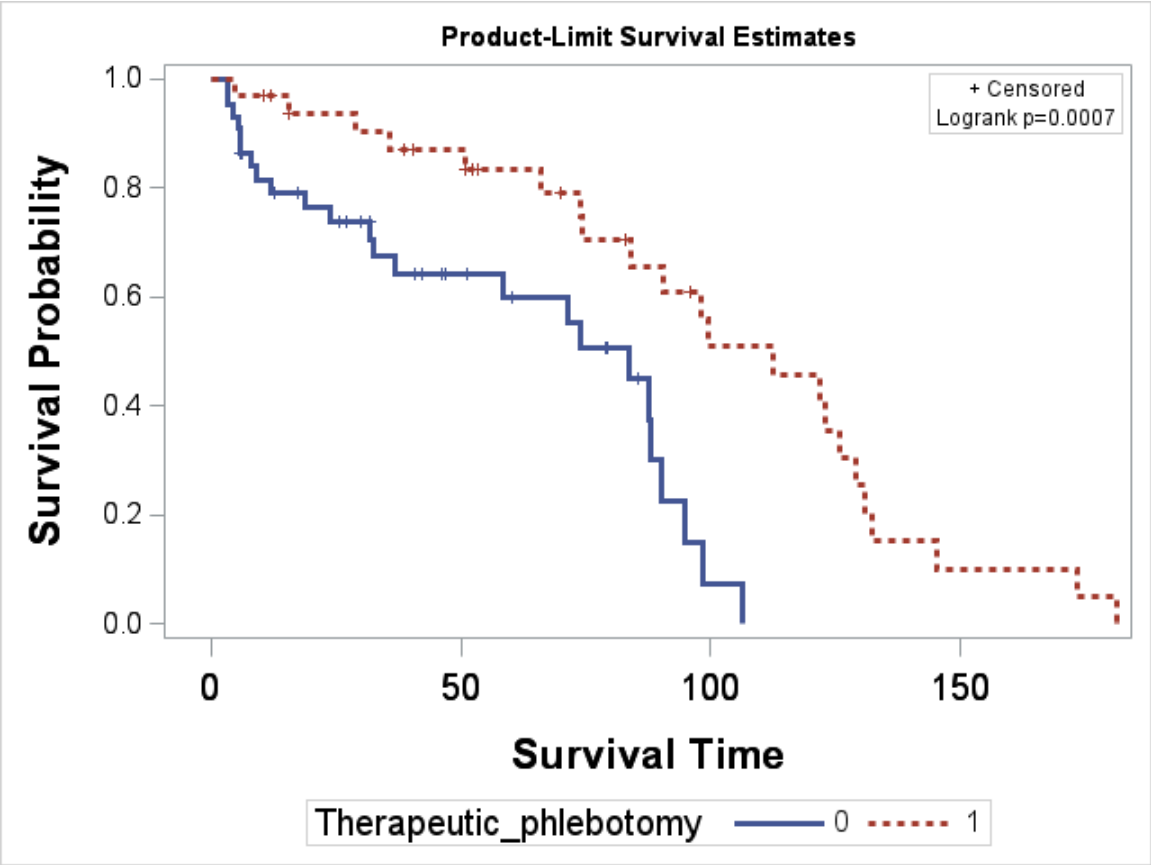


Figure 3d. Kaplan-Meier curve depicting differences in survival between male (unaltered and neutered) and female (unaltered and spayed) dogs with reverse patent ductus arteriosus.

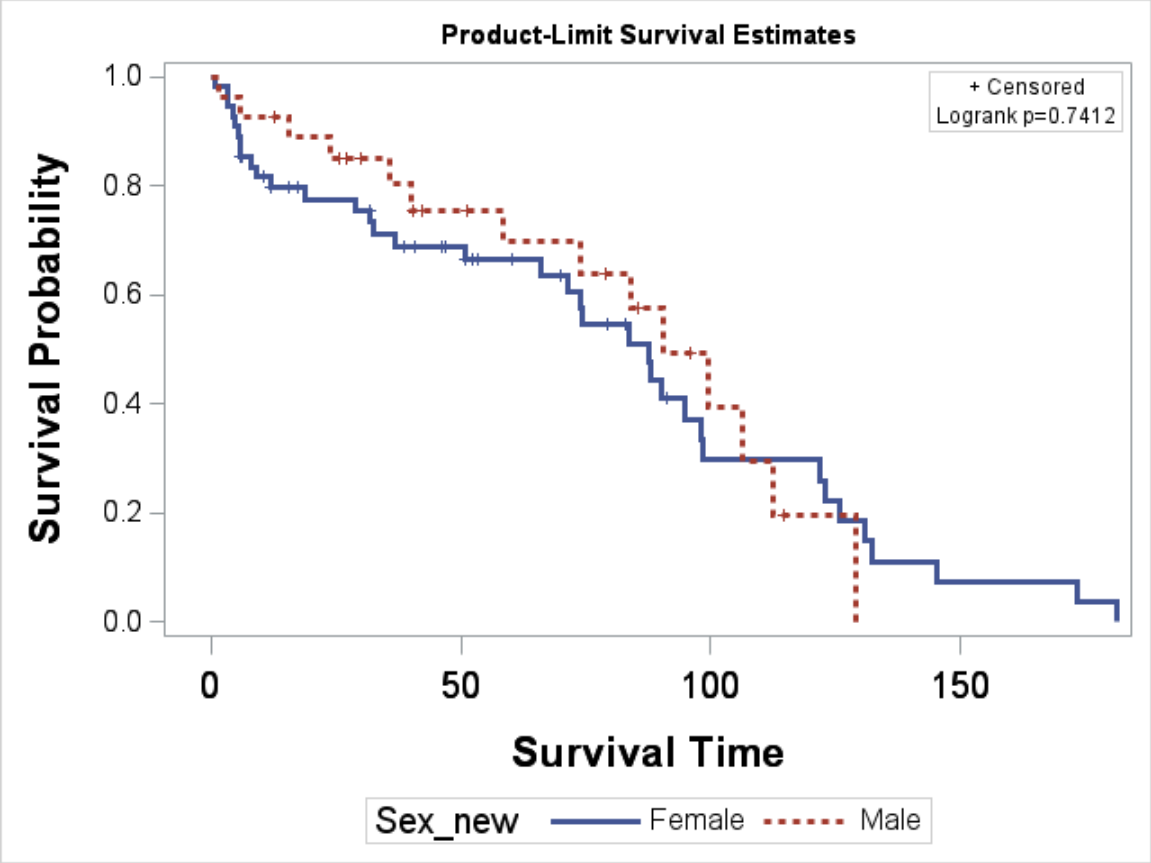


Figure 3e. Kaplan-Meier curve depicting differences in survival between unaltered male, neutered male, unaltered female, and spayed female dogs with reverse patent ductus arteriosus.

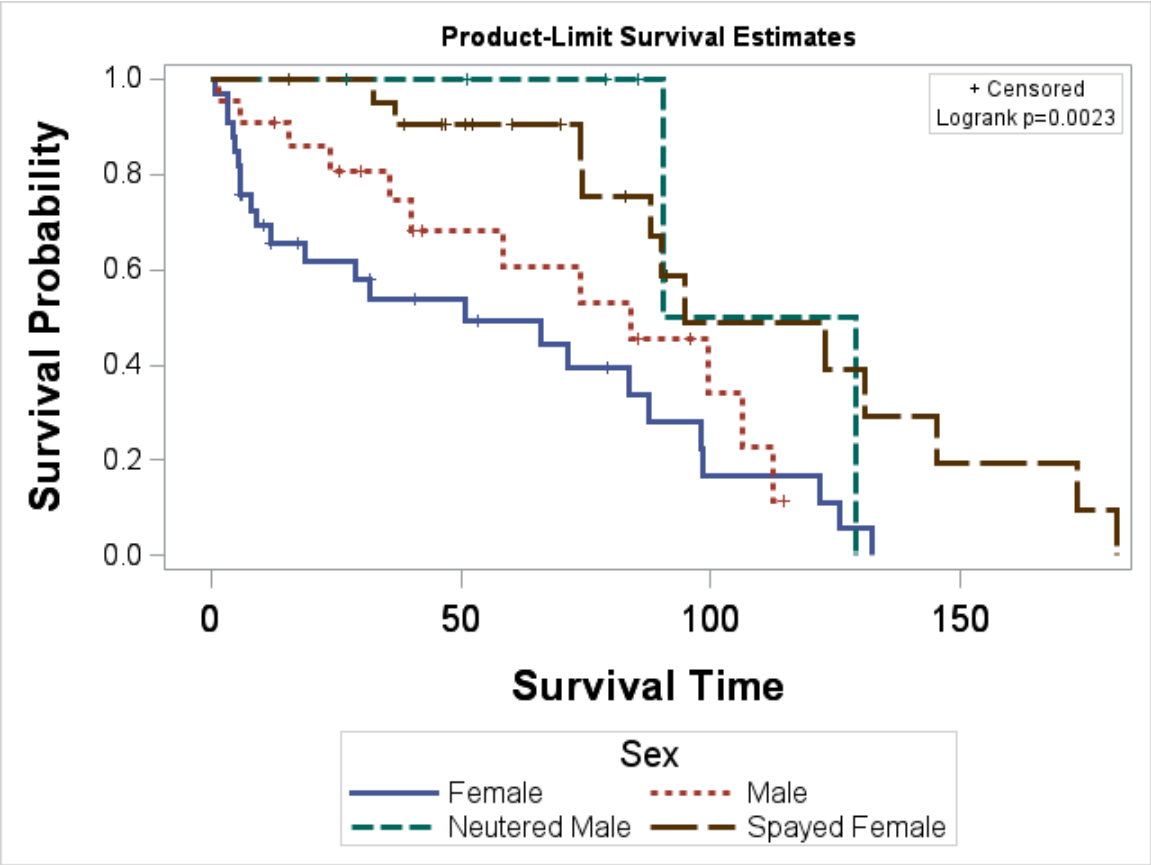
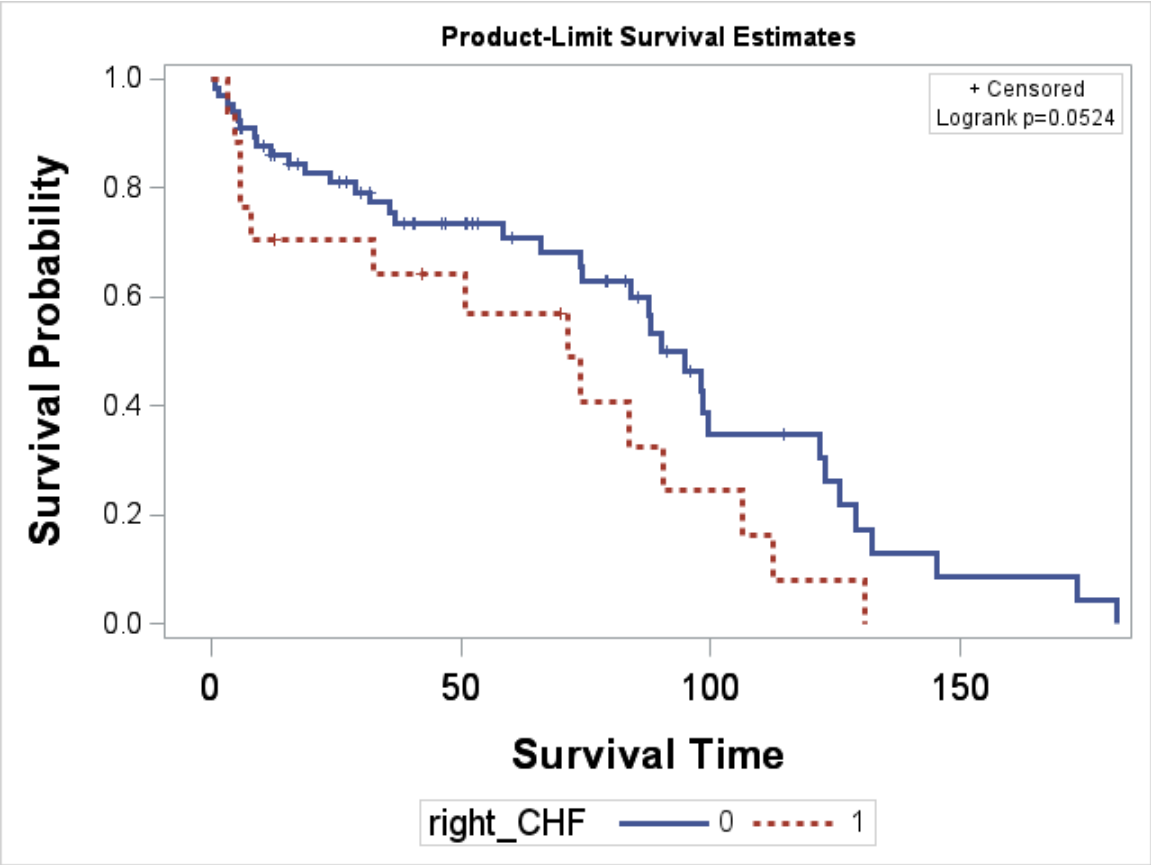


Figure 3f. Kaplan-Meier curve depicting differences in survival between dogs with reverse patent ductus arteriosus that developed right congestive heart failure (CHF) and those that did not.



APPENDIX 2: TABLES

Table 1a. Initial body condition score for dogs with reversed patent ductus arteriosus using a scale of 1-9.

Initial Body Condition Score:		
Category	Number of Dogs	%*
1	0	0%
2	0	0%
3	9	10%
4	28	32%
5	37	43%
6	9	10%
7	3	4%
8	0	0%
9	1	1%
Total	87	100%

*As percentage of dogs for which body condition score was recorded

Table 1b. Final body condition score for dogs with reversed patent ductus arteriosus using a scale of 1-9.

Final Body Condition Score:		
Category	Number of Dogs	%*
1	0	0%
2	2	2%
3	10	12%
4	24	29%
5	32	38%
6	11	13%
7	4	5%
8	1	1%
9	0	0%
Total	84	100%

*As percentage of dogs for which body condition score was recorded

Table 2a. Echocardiographic parameters in dogs with reversed patent ductus arteriosus.

Echocardiographic Findings (n=136 dogs):		
Parameter	Number of Dogs	% or Mean (+/- SD)
RV Concentric Hypertrophy	84	62%
Mild	9	7%
Moderate	22	16%
Severe	46	34%
Unspecified Degree	7	5%
RV Eccentric Hypertrophy	51	38%
Mild	2	1%
Moderate	16	12%
Severe	27	20%
Unspecified Degree	6	4%
RV Hypertrophy (Unspecified)	29	21%
Mild	1	<1%
Moderate	2	1%
Severe	24	18%
Unspecified Degree	2	1%
RA Enlargement	91	67%
Mild	17	13%
Moderate	26	19%
Severe	32	24%
Unspecified Degree	16	12%
PDA Morphology (Miller)	10	7%
I	0	0%
II (Unable to Refine)	4	3%
IIa	1	<1%
IIb	2	1%
III	3	2%
Abnormal Interventricular Septal Motion	119	88%
Paradoxical Motion	39	29%
Septal Flattening	80	59%
Doppler RV Outflow Profile	45	33%
I	16	12%
II	17	13%
III	12	9%
Tricuspid Valve Regurgitation	93	69%
Trace or Mild	52	39%
Moderate	16	12%
Severe	20	15%
Unspecified Degree	5	4%

Estimated Maximum Trans-Tricuspid Pressure Gradient (mmHg)	62	46%; 95.12 (+/- 33.2)
Estimated PGmax≥ 46.2 mmHg	58	94%*
2D Transverse Left Ventricular Internal Diastolic Dimension (mm)	81	16.9 (+/- 8.2)
M-mode Transverse Left Ventricular Internal Diastolic Dimension (mm)	13	11.9 (+/-3.9
Normalized 2D Transverse Left Ventricular Internal Diastolic Dimension**	79	1.0 (+/- 0.3)
2D Long-Axis Left Atrial Diameter (mm)	58	17.5 (+/- 6.0)
Normalized 2D Long-Axis Left Atrial Diameter**	58	1.1 (+/- 0.3)
2D Left Atrium: Aortic Root ratio	74	1.3 (+/- 0.3)
Agitated Saline Contrast Study:	96	71%

Abbreviations: SD, standard deviation; RV, right ventricle; RA, right atrium; PDA, patent ductus arteriosus; PGmax, maximum pressure gradient; M-mode, motion mode; 2D, 2-dimensional.

*As percentage of dogs with a recorded trans-tricuspid PGmax

**Allometric scaling for 2D echo variables [Visser et al]

Table 2b. Electrocardiographic parameters in dogs with reversed patent ductus arteriosus.

Electrocardiographic Findings (n=85 dogs):		
Parameter	n= Number of Dogs	% or Mean (+/- SD)
Sinus rhythm, sinus tachycardia, or sinus arrhythmia (No Ectopy)	77	91%
Right axis deviation/ Deep S-Waves in Lead II	59	69%
Right Bundle Branch Block	3	4%
Premature Atrial Ectopy	2	2%
Premature Ventricular Ectopy	1	1%

Abbreviation: SD, standard deviation

Table 3. Radiographic findings in dogs with reversed patent ductus arteriosus.

Radiographic Findings (n=90 dogs):		
Parameter**	Number of Dogs	%*
Cardiomegaly	70	78%
Right Chamber Enlargement	57	63%
Main Pulmonary Artery Enlargement	46	51%
Aortic Root Enlargement/ Ductal Bump	30	33%
Peripheral Pulmonary Artery Dilation	17	19%
Non-Cardiogenic or Ambiguous Infiltrates	17	19%
Cardiogenic Pulmonary Edema	2	2%
Pleural Effusion	2	2%

*As percentage of dogs for which thoracic radiographs were obtained

**Categories are not mutually exclusive

Table 4. Cardiovascular comorbidities in 137 dogs with reversed patent ductus arteriosus.

Cardiovascular Comorbidities		
Diagnosis*	Number of Dogs	%
None	104	76%
Tricuspid Valve Dysplasia	11	8%
Patent Foramen Ovale	6	4%
Ventricular Septal Defect	6	4%
Atrial Septal Defect	3	2%
Myxomatous Mitral Valve Degeneration	3	2%
Persistent Left Cranial Vena Cava	3	2%
Mitral Valve Dysplasia	2	1%
Dynamic Left Ventricular Outflow Tract Obstruction	1	1%
Pulmonic Stenosis	1	1%
Subaortic Stenosis	1	1%
Suspected Pulmonary Arteriovenous Malformation	1	1%
Suspected Intracardiac Thrombi	1	1%
Systemic to Pulmonary Arteriovenous Malformation	1	1%
Systolic Anterior motion of the Mitral Valve	1	1%

*Categories are not mutually exclusive

Table 5. P-values, hazard ratios (HR), and 95% confidence intervals (CI) of variables used for parsimonious multivariate analysis of all-cause survival in dogs with reversed patent ductus arteriosus. A p-value of <0.05 was considered to be statistically significant.

Parsimonious Multivariate Analysis of All-Cause Survival			
Variable	*p*-value	HR	95% CI
Age at Presentation	<0.001	0.97	0.96-0.98
Absence of rCHF	0.047	0.49	0.25-0.99
PCV≥65%	0.005	3.49	1.47-8.30
No PDEVi Therapy	0.016	2.31	1.17-4.53
No Phlebotomy	<0.001	4.05	1.77-9.27

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Chapter 3.

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