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Long-Term Outcome in Dogs with Patent Ductus Arteriosus: 520 Cases (1994–2009)

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Background: Published information regarding survival and long-term cardiac remodeling after patent ductus arteriosus (PDA) closure in dogs is limited.

Objectives: To report outcome and identify prognostic variables in dogs with PDA, and to identify risk factors for persistent remodeling in dogs with a minimum of 12 months of follow-up after closure.

Animals: Five hundred and twenty client-owned dogs.

Methods: Retrospective review of medical records of 520 dogs with PDA. Outcome was determined by contacting owners and veterinarians. Dogs with PDA closure and ≥ 12 months of follow-up were asked to return for a re-evaluation.

Results: In multivariable analysis of 506 dogs not euthanized at the time of diagnosis, not having a PDA closure procedure negatively affected survival (HzR = 16.9, $P < .001$). In 444 dogs undergoing successful PDA closure, clinical signs at presentation (HzR = 17, $P = .02$), concurrent congenital heart disease (HD) (HzR = 4.8, $P = .038$), and severe mitral regurgitation (MR) documented within 24 hours of closure (HzR = 4.5, $P = .028$) negatively affected survival. Seventy-one dogs with ≥ 12 months follow-up demonstrated a significant reduction in radiographic and echocardiographic measures of heart size ($P = 0$) and increased incidence of acquired HD ($P = .001$) at re-evaluation. Dogs with increased left ventricular size and low fractional shortening at baseline were more likely to have persistent remodeling at re-evaluation.

Conclusions and Clinical Importance: Patent ductus arteriosus closure confers important survival benefits and results in long-term reverse remodeling in most dogs. Clinical signs at presentation, concurrent congenital HD, and severe MR negatively affect survival. Increased left ventricular systolic dimensions and systolic dysfunction at baseline correlated significantly with persistent remodeling.

Key words: Canine; Congenital; Echocardiography; Interventional; Survival.

Left-to-right shunting patent ductus arteriosus (PDA) causes volume overload of the left atrium and ventricle, which leads to remodeling in the form of eccentric hypertrophy (dilatation) predisposing patients to the development of congestive heart failure.[1,2] Immediate reduction in preload and an increase in afterload are associated with effective closure of left-to-right shunting PDA and result in decreases in left ventricular size (typically diastolic more than systolic dimensions) and left atrial size, as well as a reduction in left ventricular fractional shortening (FS).[3–8] Within 6 months of PDA closure in human patients, left ventricular size continues to decrease and systolic function often improves, although recovery of systolic function can take longer, particularly in patients presenting for PDA closure as adults.[3,9,10] Additional factors that affect the degree of left ventricular reverse remodeling (normalization of size and systolic function) include low ejection fraction before PDA closure in human patients, the presence of residual ductal flow after PDA closure in human patients and dogs, and acquired heart disease (HD) in dogs.[3–5,11] Published information regarding long-term changes in cardiac size and function after PDA closure in dogs is limited. Long-term outcome generally is good after PDA closure, especially in uncomplicated cases.[1,12,13]

The purpose of this study was to report outcome and identify prognostic variables in a large cohort of dogs with PDA. An additional objective was to identify risk factors for persistent cardiac remodeling in a

Abbreviations:

ACVIM	American College of Veterinary Internal Medicine
CI	confidence interval
DMVD	degenerative mitral valve disease
FS	fractional shortening
HD	heart disease
HR	heart rate
HzR	hazard ratio
IQR	inter-quartile range
LA/Ao	left atrium-to-aorta ratio
LVIDdN	left ventricular internal dimensions in diastole normalized to body weight
LVIDsN	left ventricular internal dimensions in systole normalized to body weight
MDD	minimal ductal diameter
MR	mitral regurgitation
OR	odds ratio
PDA	patent ductus arteriosus
VHS	vertebral heart size

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subset of dogs with PDA closure and a minimum of 12 months of follow-up.

Materials and Methods

A search of the Texas A&M University Veterinary Medical Teaching Hospital's veterinary medical information system and catheterization procedures log identified 520 dogs diagnosed with PDA between July 1996 and November 2009. Baseline data recorded for each dog included breed, sex, age, body weight, presenting complaint and medication history, murmur characteristics, heart rate, the presence and type of arrhythmia, radiographic abnormalities (eg, cardiomegaly, pulmonary overcirculation, interstitial pulmonary pattern), PDA closure method, and angiographic minimal ductal diameter (MDD) when available. A murmur was classified as severe if it was graded a V or VI out of VI. Recorded clinical signs included cough, dyspnea, exercise intolerance, lethargy, and collapse. Echocardiographic data recorded included normalized left ventricular internal dimension in diastole and systole (LVIDdN, LVIDsN, respectively),[13] FS, M-mode left atrium-to-aorta ratio (LA/Ao), aortic velocity, the presence of residual flow within 24 hours of PDA closure, the presence and severity of mitral regurgitation (MR) at baseline and within 24 hours of PDA closure, and concurrent congenital or acquired HD. For the purposes of this study, MR was recorded as severe if color Doppler mapping of the regurgitant jet demonstrated filling >50% of the area of the left atrium with concurrent left atrial enlargement. Cutoffs to identify an abnormality for the following variables were FS <25%, LVIDsN >1.26 and LVIDdN >1.85.[14] Attempts were made to contact owners and referring veterinarians for survival information, and a recheck evaluation was offered to all dogs with a minimum of 12 months after PDA closure. Data collected at the follow-up evaluation consisted of date of examination, age, body weight, presenting complaint and medication history, murmur characteristics, the presence and type of arrhythmia, radiographic abnormalities (eg, cardiomegaly, pulmonary overcirculation, interstitial pulmonary pattern) and vertebral heart size (VHS).[15] A complete transthoracic echocardiogram examination was performed using a GE Vivid E9[a] ultrasound machine with an appropriately selected 3.5–10 MHz phased-array transducer. Echocardiographic data recorded included LVIDdN, LVIDsN, FS, LA/Ao, aortic velocity, the presence and severity of MR, residual ductal flow, and concurrent congenital and acquired HD. Residual ductal flow was recorded as none, trivial, mild, moderate, or severe as previously described.[16] Study approval was obtained from the Institutional Clinical Research Review Committee and written informed consent was obtained from owners.

Statistical Analysis

Median with second and third quartile (inter-quartile range [IQR]) is reported for continuous variables. Count and percent positive are reported for dichotomous variables. Paired tests to compare baseline to follow-up on those dogs with both observations were done using Wilcoxon matched-pairs signed-ranks test for continuous variables and McNemar's chi-squared test for dichotomous variables. Semiparametric Cox models were used in uni- and multivariable survival analyses where Schoenfeld residuals were used to test the proportional-hazards assumption. Estimated hazard ratios (HzR) and median survival times are reported. Two multivariable models were fit, one to determine baseline variables that affect survival and a second to determine baseline and postoperative variables collected within 24 hours of ductal closure that affect survival. Uni- and multivariable linear regression models were used to evaluate the effects of baseline parameters on cardiac remodeling at the time of follow-up, where the Shapiro-Wilks test was used to assess the normality of the residuals. Logistic regression modeling was used to estimate the effect of baseline parameters on dichotomous variables. Estimated odds ratios (OR) and probability of the outcome of interest are reported. Goodness-of-fit was assessed with the Hosmer-Lemeshow test. Significance was determined at the 5% level and 95% confidence intervals are reported. Stata MP version 12[b] was used for all data manipulation and analyses.

Results

Baseline characteristics for 520 dogs diagnosed with PDA are reported in Table 1. The most common breeds included Bichon Frise (n = 63, 12.1%), mixed (n = 55, 10.5%), Chihuahua (n = 43, 8.2%), Poodle (n = 39, 7.5%), German Shepherd (n = 30, 5.7%), Pomeranian (n = 30, 5.7%), Shetland Sheepdog (n = 24, 4.6%), Maltese (n = 23, 4.4%), and Yorkshire Terrier (n = 20, 3.8%). Eighty-four (16.2%) dogs were ≥24 months of age at presentation, with the oldest dog presenting at 148.7 months (12.4 years) of age. Three hundred eighty-four (73.8%) dogs had no reported clinical signs. A continuous left basilar murmur was documented in 481 (92.5%) dogs. Dogs without a murmur had right-to-left shunting or very small left-to-right shunting PDA. There were 15 dogs with right-to-left shunting PDA and 2 dogs with bidirectional shunting diagnosed by a combination of visualization of the PDA, color Doppler imaging, and agitated saline injections. All of the dogs with right-to-left shunting were small breed except for 1 Golden Retriever with concurrent tricuspid valve dysplasia, and the 2 most common breeds were the Yorkshire Terrier (n = 3) and Shetland Sheepdog (n = 3). Concurrent congenital HD was diagnosed in 46 (8.8%) and most often consisted of subaortic stenosis (median transaortic systolic velocity of 5.1 m/s) diagnosed by the presence of a subvalvular ridge on 2-dimensional echocardiography and persistently increased left ventricular outflow tract velocities after PDA occlusion (n = 16) or pulmonic stenosis (n = 12). Eighteen dogs had an assortment of other defects including mitral valve dysplasia, ventricular septal defect, atrial septal defect, hypoplastic left pulmonary artery with acquired bronchial artery circulation, and combinations of subaortic stenosis and pulmonic stenosis, subaortic or pulmonic stenosis and valve dysplasia, and pulmonic stenosis and ventricular septal defect. Concurrent acquired HD was diagnosed in 26 (5%) dogs and consisted of pulmonary hypertension based on an estimated right ventricular-to-right atrial pressure gradient in the absence of pulmonic stenosis (n = 14), degenerative mitral valve disease (DMVD) (n = 8), heartworm disease (n = 2), DMVD with pulmonary hypertension (n = 1), and heartworm disease with pulmonary hypertension (n = 1). Fifteen (2.9%) dogs had documented arrhythmias consisting of ventricular arrhythmias (n = 8), atrial fibrillation (n = 6), and second-degree atrioventricular block (n = 1).

Table 1. Selected baseline characteristics for 520 dogs with PDA and baseline and follow-up characteristics in 71 dogs with >1 year of follow-up after PDA closure.

	All Dogs		71 Dogs			
	Baseline		Baseline with Follow-up		Follow-up	
Parameter	N	Median (IQR) or N (% Present)	N	Median (IQR) or N (% Present)	Median (IQR) or N (% Present)	*P* Value
Age (month)	517	5.1 (3.3–13.4)	71	7.5 (3.7–20.1)	65.3 (49.0–86.3)	0
Weight (kg)	518	3.6 (1.8–7.8)	71	4.9 (2.7–11.3)	8.2 (4.8–24.1)	0
Large breed	520	105 (20.2%)	71	15 (21.1%)	15 (21.1%)	1
Female	520	380 (73.1%)	71	50 (70.4%)	50 (70.4%)	1
HR	433	136 (120–160)	60	127 (110–151)	110 (90–130)	0
On medication	520	51 (9.8%)	71	8 (11.3%)	8 (11.3%)	1
Lethargy	520	18 (3.5%)	71	5 (7.0%)	2 (2.8%)	.453
Dyspnea or cough	520	70 (13.5%)	71	8 (11.3%)	2 (2.8%)	.109
Lethargy/dyspnea/cough	520	15 (2.9%)	71	1 (1.4%)	1 (1.4%)	1
Murmur	520	493 (94.8%)	71	71 (100.0%)	17 (23.9%)[b]	0
Murmur severe[a]	507	384 (75.7%)	69	59 (85.5%)	4 (5.8%)[b]	0
Congenital HD	520	46 (8.8%)	71	6 (8.5%)	2 (2.8%)	.125
Acquired HD	520	26 (5.0%)	71	2 (2.8%)	16 (22.5%)	.001
Pulmonary hypertension	520	16 (3.0%)	71	1 (1.4%)	16 (22.5%)	0
Arrhythmia	520	15 (2.9%)	71	7 (9.9%)	7 (9.9%)	1
AF	520	6 (1.2%)	71	0 (0.0%)	0 (0.0%)	1
Ventricular arrhythmia	520	8 (1.5%)	71	6 (8.5%)	4 (5.6%)	.727
Radiography						
VHS	63	11.5 (10.9–12.5)	62	11.5 (10.9–12.5)	10.5 (10.0–10.8)	0
Cardiomegaly(VHS > 10.5)	69	58 (84.1%)	64	53 (82.8%)	27 (42.2%)	0
Overcirculation	69	52 (75.4%)	65	49 (75.4%)	1 (1.5%)	0
Pulmonary edema	69	21 (30.4%)	65	20 (30.8%)	0 (0.0%)	0
Echocardiography						
LVIDdN	405	2.11 (1.80–2.40)	66	2.15 (1.85–2.37)	1.50 (1.40–1.70)	0
LVIDsN	405	1.27 (1.07–1.55)	66	1.33 (1.02–1.59)	1.00 (0.87–1.20)	0
FS (%)	405	0.37 (0.32–0.41)	66	0.37 (0.32–0.41)	0.28 (0.23–0.37)	0
LA/Ao	331	1.34 (1.18–1.56)	54	1.46 (1.17–1.62)	1.23 (1.11–1.31)	0
Aortic velocity	336	1.83 (1.49–2.39)	58	1.97 (1.52–2.48)	1.30 (1.05–1.53)	0
MR	426	256 (60.1%)	69	50 (72.5%)	28 (40.6%)	0
MR severe[c]	424	72 (17.0%)	69	11 (15.9%)	5 (7.2%)	.18
PDA MDD	226	2.00 (1.5–3.0)	41	2.10 (1.50–3.20)		
Residual flow	357	93 (26.1%)	69	10 (14.5%)	4 (5.6%)	.031
MR 24 hours	324	171 (52.8%)	68	42 (61.8%)		
MR severe 24 hours	324	34 (10.5%)	68	7 (10.3%)		

Median (IQR) or percentage is reported. N, number of dogs; HR, heart rate; HD, heart disease; VHS, vertebral heart size; LVIDdN, left ventricular internal dimensions in diastole normalized to body weight; LVIDsN, left ventricular internal dimensions in systole normalized to body weight; FS, fractional shortening; LA/Ao, left atrium-to-aorta ratio; MR, mitral regurgitation; PDA, patent ductus arteriosus; MDD, minimal ductal diameter; IQR, interquartile range.

[a]Murmur severe = murmur grade V or VI out of VI.

[b]Murmurs were systolic from valvular stenosis or degenerative mitral valve disease.

[c]MR severe = regurgitant jet filling ≥50% of the area of the left atrium with left atrial enlargement.

Patent ductus arteriosus closure procedures were attempted in 456 of the 513 dogs with left-to-right shunting PDA (88.9%) and consisted of 179 ligations (39.3%) and 277 catheter-based procedures (60.7%) using an assortment of devices including embolization coils (n = 187), Amplatz Canine Duct Occluders (n = 59), and Amplatzer vascular plugs (n = 31). There were 2 deaths during anesthesia, but before starting a procedure. Eleven dogs (2.4%) had a second procedure to correct residual ductal flow. Seven of the 11 dogs had 2 coil embolization procedures and 4 had a ligation followed by a coil embolization procedure. All 11 dogs survived a second procedure with resolution of residual flow in 8. The mortality rate within the first 3 days in all 456 dogs was 2.6% (n = 12). Excluding the 2 dogs that died before starting a procedure, mortality rate was not significantly different between catheter-based (5/276, 1.8%) and surgical (5/178, 2.8%, $P = .5$) closure. Nine of the 12 dogs died in the intra- or perioperative period and the remaining 3 dogs died or were euthanized 1–3 days after the procedure. Reported causes of death included complications during catheter-based procedures (eg, embolized coil, perforated artery) and cardiac arrest during or immediately after a ligation procedure (n = 5), postoperatively after Amplatz Canine Duct Occluder placement, and immediately after anesthetic induction before a planned catheter-based procedure. PDA closure was

not attempted in 64 (12.5%) dogs for various reasons including right-to-left shunting, small PDA considered to be hemodynamically inconsequential, or most often because the owners declined or elected euthanasia (Fig 1).

At the time of writing, 438 of the 520 dogs (84.2%) were alive or lost to follow-up at a median age of 38.6 months (range 1.2–196.0 months) and 82 (15.8%) dogs were dead at a median age of 26 months (range 1.0–191.1 months). The cause of death was categorized as cardiac in 44/82 (53.6%) of which 9 were euthanized at presentation, noncardiac in 20/82 (24.4%) of which 1 was euthanized at presentation, and unable to be determined in 18/82 (22.0%). Survival time ranged from 1 day to 193.2 months (median, 25.1 months) for the 456 dogs that had ductal closure attempted. For the 64 dogs that did not have closure, 37 survived <1 day because of owner elected euthanasia (range 1 day - 67.3 months).

Survival Analysis

In separate univariate analyses on the survival time of the most common breeds, the estimated HzR for not having a PDA closure were as follows: mixed (n = 3/55, HzR = 3.7, $P = .002$, power to detect a HzR of that size = 99%), Poodle (n = 5/36, HzR = 2.5, $P = .006$, power = 95%), Pomeranian (n = 1/30, HzR = 3.3, $P = .021$, power = 81%), German Shepherd (n = 3/30, HzR = 1.9, $P = .128$, power = 75%), and Chihuahua (n = 4/43, HzR = 1.6, $P = .067$, power = 56%), where n is the number without PDA closure/number of the breed. Other common breeds had insignificant HzR or the ratios were not estimable: Bichon Frise (n = 1/62), Maltese (n = 3/23), Yorkshire Terrier (n = 4/19), and Shetland Sheepdog (n = 2/23).

In a multivariable analysis of the 506 dogs that had a left-to-right shunting PDA and were not euthanized at the time of diagnosis, both not having a PDA closure procedure (HzR = 16.9, $P < .001$) and the presence of concurrent congenital HD at baseline (HzR = 5.2, $P < .001$) had a negative effect on survival. For a dog without concurrent congenital HD, PDA closure adds an estimated 10 years to the median lifespan (12 years compared with 2 years of median survival time), but for a dog with concurrent congenital HD, only 4 years of additional survival time can be expected with PDA closure (6 years compared with 2 years of median survival time).

Left atrium-to-aorta ratio was significant (OR = 9.6, $P = .003$) in a univariate logistic regression model that utilized perioperative mortality (12/456) as the response variable. The predicted risk of perioperative death increased from 2% when the LA/Ao was 1.5 to 20% when it was 2.5.

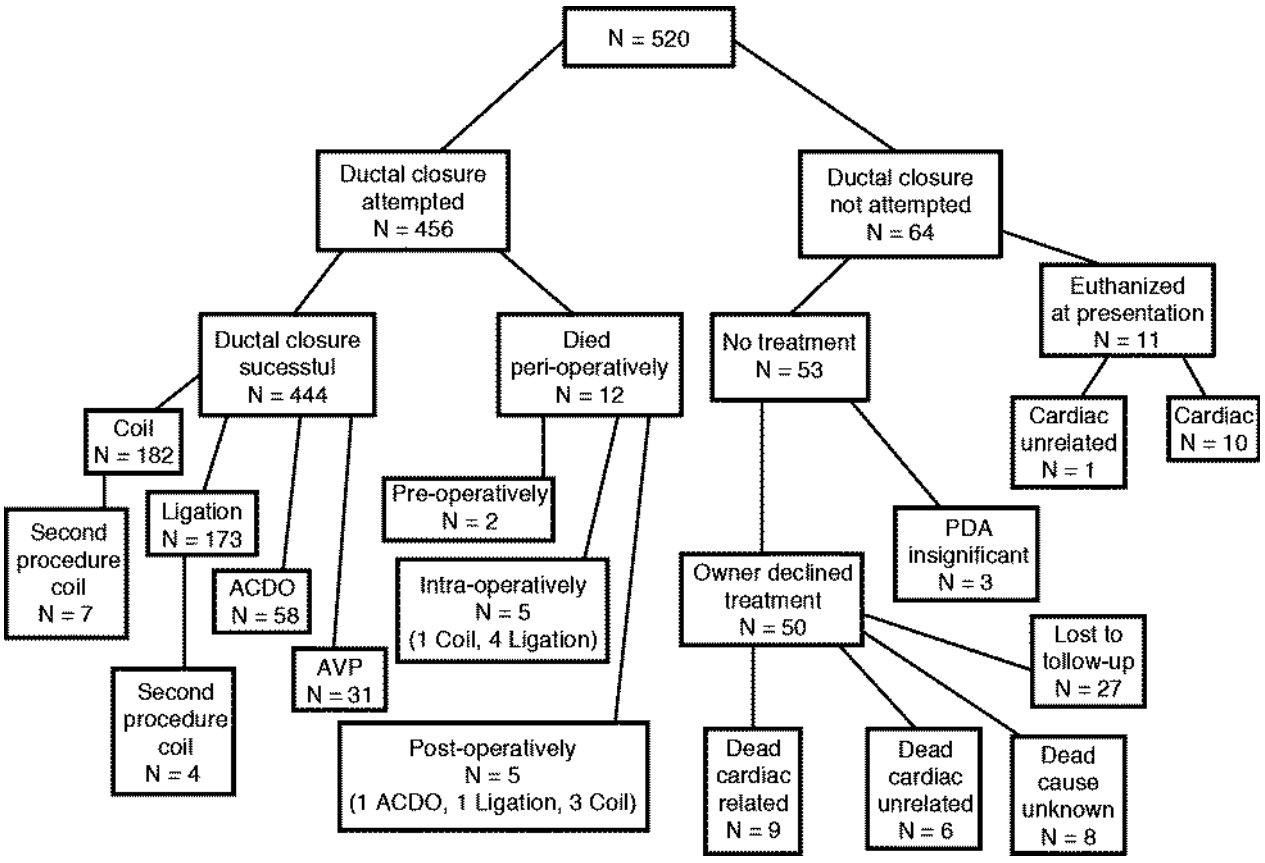

Fig 1. A flow chart indicating the outcome for 520 dogs with PDA. ACDO, Amplatz Canine Duct Occluder; AVP, Amplatzer vascular plug; PDA, patent ductus arteriosus.

Estimated HzR from univariate analyses of baseline variables on survival time in the 444 dogs that had successful PDA closure are shown in Figure 2, which displays the 8 parameters that were significant at the 10% level or lower. The presence of clinical signs (eg, lethargy, cough, dyspnea) was associated with decreased survival time (HzR = 10, $P = .03$). Concurrent congenital HD (HzR = 7.9, $P = .0001$), large breed (HzR = 3.2, $P = .001$), age (HzR = 1.1 per 6 months increase, $P = .01$), weight (HzR = 1.2 per 5 kg increase, $P = .02$), and severe MR documented within 24 hours of ductal closure (HzR = 5.2, $P = .003$) also had significant negative effects on survival.

In the parsimonious multivariable analysis of the dogs that underwent successful PDA closure (n = 444), clinical signs at presentation (eg, lethargy, cough, dyspnea) (n = 314, HzR = 17, $P = .02$), concurrent congenital HD (HzR = 4.8, $P = .038$), and severe MR documented within 24 hours of ductal closure (HzR = 4.5, $P = .028$) remained significant and were associated with decreased survival time. Median post-PDA closure survival times estimated from the multivariable model are shown in Figure 3. Based on this model, a dog with clinical signs (eg, lethargy, cough, dyspnea), concurrent congenital HD, and severe MR documented within 24 hours of PDA closure would be expected to have a median survival time of 1 month (95% CI, 0–1 year) after PDA closure. A dog with clinical signs (eg, lethargy, cough, dyspnea) and concurrent congenital HD would be expected to have a median survival time of 9 years (95% CI, 2.6–10 years), whereas a dog with none of these would be expected to have a median survival time of 15 years.

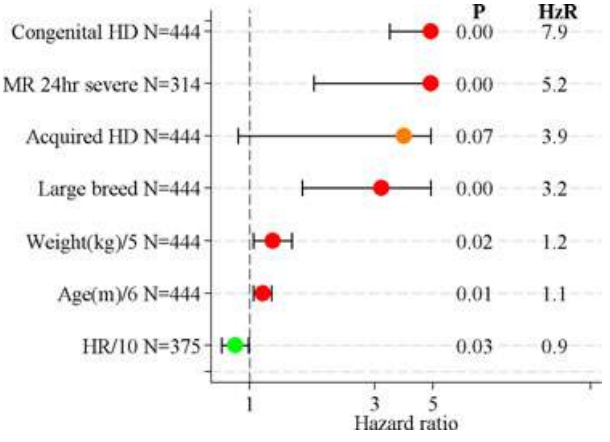

Fig 2. Estimated hazard ratios with 95% confidence intervals from univariate analyses of baseline parameters on survival time in 444 dogs that had successful patent ductus arteriosus closure. Continuous variables have been scaled for analysis to preserve clinical significance of any changes. For example, for weight, a 1-unit change was considered to be 5 kg, whereas for age, a 1-unit change was considered to be 6 months. HD, heart disease; MR 24hr, mitral regurgitation within 24 hours of ductal closure; m, months; HR, heart rate; HzR, hazard ratio.

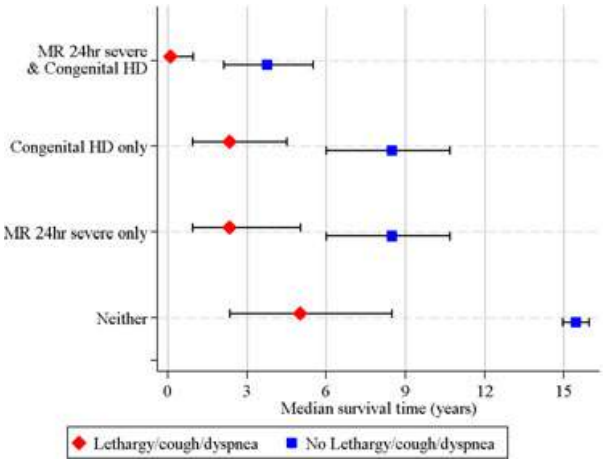

Fig 3. Estimated median survival time for dogs with successful patent ductus arteriosus closure from multivariable analyses of effect of baseline parameters on survival time (semiparametric Cox regression) with 95% confidence intervals (n = 314). MR 24 hr, mitral regurgitation within 24 hours of ductal closure; HD, heart disease.

Left atrium-to-aorta ratio (OR = 7.2, $P = .009$), LVIDsN (OR = 4.1, $P = .026$), and concurrent acquired HD (OR = 13.5, $P = .016$) were significant in a multivariable logistic regression model that utilized severe MR documented within 24 hours of ductal closure as the response variable (n = 244). This indicates that both left heart enlargement and concurrent acquired HD are associated with increased probability of severe MR within 24 hours of ductal closure.

Dogs with PDA Closure and a Minimum of 12 Months of Follow-up

Baseline characteristics for 71 dogs with PDA closure and a minimum of 12 months of follow-up are reported in Table 1. Breeds represented included Chihuahua (n = 10, 14%), mixed (n = 9, 13%), Bichon Frise (n = 7, 9.8%), German Shepherd (n = 5, 7%), Shetland Sheepdog (n = 4, 5.6%), Pomeranian (n = 4, 5.6%), and 1 each of 33 additional breeds. Fifteen dogs (21%) were 24 months of age at presentation with a median age of 46 months (range 26.6–97.9 months). At the time of the initial evaluation, 16 dogs (22%) presented with clinical signs including cough (n = 8), exercise intolerance (n = 5), cough and exercise intolerance (n = 1), and collapse or seizure-like activity (n = 2). Eight dogs were receiving cardiac medications at presentation as follows: furosemide (n = 2), angiotensin-converting enzyme inhibitor (n = 1), furosemide and angiotensin-converting enzyme inhibitor (n = 3), furosemide and pimobendan (n = 1), amlodipine (n = 1). All dogs had a characteristic left basilar continuous murmur consistent with a left-to-right shunting PDA. Six dogs (8%) had concurrent congenital HD, which included subaortic stenosis (n = 3), pulmonic stenosis (n = 1), and mitral valve dysplasia (n = 2). Two dogs (1%), both of which were

older than 24 months, had concurrent acquired HD, which included DMVD classified as American College of Veterinary Internal Medicine (ACVIM) stage B1[17] (n = 1) and pulmonary hypertension based on an estimated right ventricular-to-right atrial pressure gradient of 90 mmHg in the absence of pulmonic stenosis (n = 1). In this dog, the PDA was shunting left-to-right and PDA closure was performed with subsequent resolution of pulmonary hypertension. Arrhythmias were documented in 7 dogs (9%) and consisted of ventricular arrhythmias (n = 6) and second-degree atrioventricular block (n = 1).

Closure methods included surgical ligation (n = 28, 39.4%) and catheter-based procedures (n = 43, 60.6%) with devices including embolization coils (n = 18), Amplatz Canine Duct Occluders (n = 18), and Amplatzer vascular plugs (n = 7). One dog had clinically relevant residual ductal flow after a coil embolization procedure, and a second coil embolization procedure was performed within a month resulting in resolution of long-term residual ductal flow.

Median time from initial evaluation to follow-up was 48.9 months (range 13.0–125.3 months). Five dogs (7%) presented with clinical signs at re-evaluation including cough (n = 3) and exercise intolerance (n = 2), which were not related to the PDA. Two dogs had abnormal thoracic radiographic findings including a large primary pulmonary mass and congestive heart failure secondary to a combination of severe subaortic stenosis and aortic valve endocarditis. Eight dogs were receiving cardiac medications at follow-up including atenolol for subaortic stenosis (n = 2) and standard medical treatment for heart failure (n = 1). Five dogs were receiving cardiac medications that were determined to be unnecessary and were discontinued. Seventeen dogs (23.9%) had a left basilar or apical systolic murmur. A continuous murmur was not auscultated in any of these dogs. Sixteen dogs (22%) had concurrent DMVD classified as ACVIM stage B1 (n = 14) and stage B2 (n = 2). The median age of dogs with DMVD was 84.3 months (range 50.0–129.3 months), and all but one of these dogs had trivial-to-mild MR. Arrhythmias were documented in 7 dogs (9%), 3 of which had arrhythmias present at initial evaluation, and consisted of ventricular arrhythmias (n = 5), ventricular arrhythmias and supraventricular premature beats (n = 1), and second-degree atrioventricular block (n = 1). Median MDD for 41 dogs with angiograms performed and for which ductal diameter was recorded was 2.1 mm (range 0.8–5.4 mm).

One dog was excluded from further statistical analysis because echocardiographic data were unavailable. Selected radiographic and echocardiographic parameters are reported in Table 1 and documented significant reductions in VHS, LVIDdN, LVIDsN, LA/Ao, aortic velocity, and FS ($P = .0001$ for all variables) at follow-up when compared with baseline values. Initial radiographic findings included pulmonary overcirculation in 51/68 (75%) and pulmonary interstitial pattern in 20/65 (30.8%) that were no longer present at follow-up. At follow-up, pulmonary venous distension was identified in 1 dog with subaortic stenosis and aortic endocarditis.

Paired radiographic and echocardiographic results are reported in Table 1 and document a significant decrease in heart size. VHS was >10.5 in 51/68 (75.0%) at baseline and in 18/70 (25.7%) at follow-up. The LVIDdN was >1.85 in 53/66 (80.3%) at baseline and in 6/70 (8.5%) at follow-up. The LVIDsN was >1.26 in 35/66 (53.0%) at baseline and in 11/70 (15.7%) at follow-up. Of the 11 dogs with persistently increased LVIDsN, 1 had mild residual ductal flow and 7 had concurrent DMVD. FS was <25% in 4/68 (5.8%) at baseline and in 22/70 (31.4%) at follow-up. Two of the 4 dogs with initial FS <25% had values of 23–24% and all 4 dogs had FS >25% by the follow-up evaluation. Fourteen of 22 dogs with FS <25% at follow-up were large breed and 5/14 had FS between 20 and 25%. Four dogs had LVIDdN >1.85 and LVIDsN >1.26 and FS <25% at re-evaluation, without any historical or clinical abnormalities documented.

Residual flow was documented in 9 dogs (12%) within 24 hours of PDA closure and in 4 dogs (5%) at long-term follow-up. Residual flow at follow-up was characterized as trivial to mild, persistent (not new), and was documented in dogs that underwent coil embolization (n = 3) or surgical ligation (n = 1) procedures. Recanalization and delayed device embolization were not documented in any dog.

Results of the univariate linear regression analysis of the effect of baseline parameters on heart size and function at re-evaluation are listed in Table 2. Baseline age, weight, large breed, increased left ventricular size, decreased FS, PDA MDD, and residual ductal flow within 24 hours of ductal closure were significantly associated with increased heart size and decreased FS at follow-up. Only baseline VHS was significantly associated with VHS at re-evaluation. Of the parameters associated with left ventricular size (LVIDdN, LVIDsN), baseline LVIDsN was the most significant predictor of re-evaluation heart size and systolic function assessed by FS.

Multivariable linear regression analyses were used to identify predictors of left ventricular size and function at follow-up. Numerous models using subsets of variables, together with interactions, were fit to identify those combinations with greatest significance, and ultimately 2 models were identified. For re-evaluation LVIDsN, baseline LVIDsN ($P < .001$), age ($P = .018$), weight, and murmur grade ≤IV were significant (n = 65). In particular, increased LVIDsN at baseline was associated with increased LVIDsN at re-evaluation. A significant positive interaction between weight and LVIDsN ($P < .001$) indicated that the link between baseline and re-evaluation LVIDsN was intensified for heavier dogs. The negative interaction between murmur grade ≤IV and LVIDsN ($P = .008$) indicated that the link between baseline and re-evaluation LVIDsN was intensified for dogs with lower grade murmurs. Because age and weight were significant, estimated means

Table 2. Univariate linear regression analyses of effect of selected baseline parameters on re-evaluation heart size and function in 71 dogs with >1 year of follow-up after PDA closure.

	LVIDdN Recheck			LVIDsN Recheck with Follow-up		FS Recheck		VHS Recheck		
Baseline Parameter	N	Coef or N (% present)	*P*	Coef or N (% present)	*P*	Coef	*P* or N (% present)	N	Coef	*P*
Age (month)/6	70	0.03	0	0.03	0	−0.91	0.01	66	0.02	.54
Weight (kg)/5	70	0.05	0	0.07	0	−2.83	0	66	0.03	.62
Large	70	0.07	.35	0.13	.08	−7.88	0.01	66	−0.04	.85
Female	70	−0.07	.32	−0.02	.79	−1.95	0.47	66	−0.02	.92
HR/10	59	−0.02	.03	−0.02	.02	0.76	0.08	55	−0.04	.17
Murmur severe	68	−0.14	.09	−0.1	.26	−1.4	0.69	64	−0.07	.75
MR severe	68	0.03	.68	0.14	.09	−8.96	0.01	64	0.15	.50
Congenital HD	70	0.14	.19	−0.06	.57	7.77	0.08	66	0.36	.24
Acquired HD	70	0.42	.02	0.58	0	−16.19	0.03	66	1.21	.01
Arrhythmia	70	0.03	.73	0.16	.11	−9.54	0.02	66	−0.14	.61
VHS	63	0.01	.81	0.06	.05	−3.42	0	62	0.21	0
LVIDdN	66	0.07	.18	0.14	.01	−6.31	0.01	62	0.15	.24
LVIDsN	66	0.15	.05	0.25	0	−11.02	0	62	0.23	.20
FS%/5	66	−0.05	.01	−0.08	0	3.21	0	62	−0.06	.24
LA/Ao	57	0.17	.14	0.22	.06	−8.54	0.07	55	0.01	.96
Aortic velocity	58	0.02	.53	−0.01	.7	0.9	0.49	55	0.12	.08
PDA MDD	40	0.06	.05	0.08	0	−3.21	0	36	−0.01	.94
Residual flow	68	0.36	0	0.33	0	−4.98	0.18	64	0.59	.03
MR 24 hours	68	0.11	.09	0.08	.19	−0.75	0.77	64	0.39	.02
MR severe 24 hours	68	−0.05	.64	0.01	.9	−5.31	0.2	64	0.36	.21

N, number of dogs; Coef, coefficient; HD, heart disease; VHS, vertebral heart size; LVIDdN, left ventricular internal dimensions in diastole normalized to body weight; LVIDsN, left ventricular internal dimensions in systole normalized to body weight; FS, fractional shortening; LA/Ao, left atrium-to-aorta ratio; MR, mitral regurgitation; PDA, patent ductus arteriosus; MDD, minimal ductal diameter.

shown in Figure 4 are for a fixed age (baseline 5 months) and weight (baseline 5 or 20 kg). These values were selected for the purposes of visualization only. Similar trends would be seen at different ages and weights.

In the multivariable model of re-evaluation FS, baseline FS, weight and severe MR were significant (n = 65). Low FS at baseline was significantly associated with low FS at re-evaluation ($P = .002$). Heavier dogs at baseline had significantly lower FS at re-evaluation ($P = .002$). The significant negative interaction between severe baseline MR ($P = .005$) indicated that dogs with severe MR have, on average, lower FS on re-evaluation when compared with dogs without severe MR. Because weight was significant in this model, Figure 4 shows estimated means for dogs at 2 weights: 5 kg and 2 kg.

Discussion

In this study, the majority of dogs were young (median age, 5.1 months), female (73.1%), small breed (79.8%), had a characteristic left base continuous murmur (94.8%), and had no reported clinical signs (73.8%) at the time of PDA diagnosis. The large number of females and young age of the dogs was consistent with high prevalence rates in females ranging from 71.1 to 78.5%[6,12,18–20] and median age at diagnosis ranging from 4 to 7 months.[6,20,21] Twenty-one percent of dogs in this study were older than 24 months at the time of initial diagnosis, similar to 21 to 25.5% of dogs in previous reports.[21,22] Age at presentation has been associated with persistent remodeling in humans with PDA,[3] and was significant in univariate analysis in this study. In multivariable analysis, LVIDdN was significantly larger in older dogs at re-evaluation in this study. The median weight of dogs in this study was 3.6 kg, which is lower than previously reported median weights that ranged from 5.0 to 17.6 kg[6,20,21] and is likely related to the large number of small breed dogs in this study. Breeds in this study were similar to previous reports, although Bichon Frise was the most common breed, which was likely related to the authors' relationship with a rescue organization. Chihuahuas represented the third most common breed and although they are a recognized breed at risk for PDA,[23,24] they have not been previously listed in the most common breeds affected.[6,18–20,25]

Published long-term survival information after PDA closure is limited in dogs. This is likely due in part to the perception that many dogs do well clinically after PDA closure, particularly in uncomplicated cases without residual flow or concurrent HD.[1,12,13] One- and 2-year survival rates after PDA ligation are 92 and 87%, respectively.[18] Median survival in 24 dogs with uncomplicated PDA was >11.5 years after ductal occlusion.[13] In 1 study, maximum survival time was significantly longer with PDA closure (168 months) compared with dogs that were not occluded (114 months).[5] Without PDA closure, 9 of 14 dogs survived <1 year after diagnosis.[19] General guidelines for follow-up after PDA closure in humans include re-evaluation within

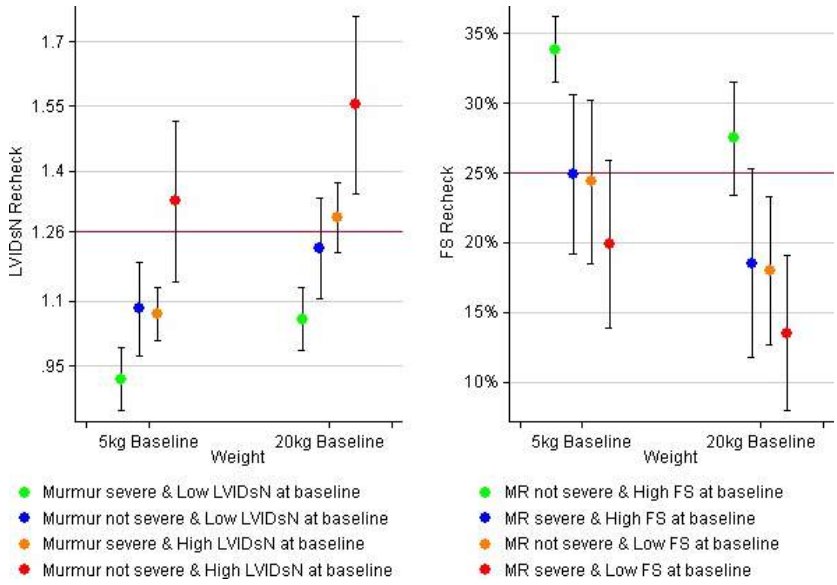

Fig 4. Estimated means from multivariate linear regression analyses of the effect of baseline parameters on recheck heart size and function (LVIDsN N = 65 and FS N = 66), with 95% confidence intervals (Low baseline LVIDsN = 1.0, High baseline LVIDsN = 1.6. Low baseline FS = 20%, High baseline FS = 40%) for a dog 5 months of age. LVIDsN, left ventricular internal dimensions in systole normalized to body weight; FS, fractional shortening. Murmur severe indicates a murmur grade V or VI out of VI.

6 months often with no further evaluation required after 12 months if the ductus arteriosus is completely closed.[26,27] More specific long-term re-evaluation schedules are recommended for adults with PDA, those patients with concurrent congenital or acquired HD or residual ductal flow, and to monitor patients with devices, which have limited long-term outcome information.[27]

Studies reporting survival characteristics are predominately retrospective and vary between short- and long-term survival, methods of statistical analysis, and treatment methods (surgical or catheter-based). In our study survival analysis demonstrated that not having a procedure to close a PDA negatively affects survival time (HzR = 16.9, $P < .001$). In dogs that had surgical or catheter-based closure of a PDA, the presence of clinical signs (eg, lethargy, cough, dyspnea) at presentation, concurrent congenital HD, and severe MR within 24 hours of PDA closure were predictors of shorter survival time. Age, weight, and large breed were associated with decreased survival time in univariate analysis, but were not maintained in multivariable analysis. Previous studies have reported mixed results. An increased rate of intra-operative death during PDA ligation was observed in dogs >2 years of age and >23 kg.[19] Long-term survival was negatively affected by age, weight, lethargy, preoperative treatment with angiotensin-converting enzyme inhibitors, and right atrial enlargement on thoracic radiographs in a univariate analysis of 52 dogs.[18] In other studies, survival was not affected by age >12 months at diagnosis, age >24 months at diagnosis, baseline FS ≤30%, weight, or the presence of residual flow at discharge.[5,18,25] Dogs with clinical signs of heart failure have had variable outcomes reported including no effect on survival to more likely to have an unsuccessful ligation procedure and die perioperatively.[18,25] Likewise, the presence of MR at baseline evaluation has been associated with variable outcomes including no effect or a questionable effect on survival that did not reach significance in statistical analysis.[5,18] When combined with atrial fibrillation or congestive heart failure, MR identified by auscultation at the time of surgery has been associated with shorter survival time.[18] Previous studies have analyzed MR at the time of presentation and have utilized a combination of auscultation, echocardiography, or both to diagnose MR.[5,18] In our study, both baseline MR and MR documented within 24 hours of PDA closure were analyzed. Baseline MR in combination with LVIDsN above the reference range, FS <25%, large breed, and a murmur grade ≤IV was associated with persistently increased LVIDsN and low FS at follow-up. In the multivariable model, it may seem counterintuitive that a softer murmur was associated with persistent remodeling. A softer murmur may have led to delayed diagnosis and referral for definitive PDA closure. The presence of severe MR (jet filling >50% of the left atrium and left atrial enlargement) within 24 hours of PDA closure negatively affected survival time. In addition, severe MR documented within 24 hours of PDA closure was more likely to be present in dogs with left heart enlargement, specifically LVIDsN, and concurrent acquired HD that included DMVD. MR documented after PDA closure is likely more important than that observed at presentation because the expected reduction in heart size after PDA closure should result in a decrease or resolution of functional MR, and persistent MR after PDA closure may contribute to volume overload leading to progressive left atrial and left

ventricular dilatation or perhaps even valvular endocardiosis.[1,5,28]

Concurrent congenital HD was identified in 8.8% of dogs and most often was subaortic stenosis or pulmonic stenosis similar to previous reports.[6,20,28] Increases in left ventricular outflow tract velocities occur secondary to increased volume to the left side of the heart associated with the PDA, and velocities decrease after ductal closure.[5,7,20] Subaortic stenosis was confirmed by documentation of 2-dimensional structural abnormalities in the left ventricular outflow tract and persistently increased velocities after PDA closure. Combinations of valve stenosis, septal defects, and valve dysplasia also were identified. Concurrent congenital HD could negatively affect survival by contributing to cardiac remodeling and by altering owners' perceptions or decisions regarding their dogs' HD and quality of life.

The immediate effects of PDA closure include an abrupt decrease in preload resulting in a decrease in left atrial and left ventricular size.[3,6] A concurrent increase in afterload associated with increased systemic vascular resistance often contributes to a greater decrease in left ventricular diastolic rather than systolic dimensions resulting in decreased indices of systolic function.[3,6] Over time in humans, left ventricular remodeling tends to continue to improve, but may not normalize depending on specific characteristics at initial evaluation that include age at the time of closure, left ventricular systolic dysfunction, and PDA size as well as the presence and degree of residual flow after ductal closure.[3,4] In our study, LVIDdN, LVIDsN, LA/Ao, and VHS decreased significantly over the long-term follow-up period (median, 48.9 months). At follow-up, 8.5% of dogs had LVIDdN >1.85 and 15.7% had LVIDsN >1.26. Another study reported an initial decrease in LVIDd, LA/Ao, and FS with continued long-term improvement in LVIDd indexed to body weight documented in 31 dogs over a mean time of 26 months despite residual flow in 12 (39%).[6] After transvenous coil embolization in 28 dogs, LVIDd indexed to body weight decreased significantly in the long term in most dogs, but remained increased in some dogs with varying degrees of MR.[11] In 24 dogs with uncomplicated PDA, LVIDd indexed to body weight returned to reference range at 3 months with a more gradual decrease in LVIDs indexed to body weight to the upper end of the reference range at 12 months after PDA occlusion. Persistent systolic dysfunction documented in more than half of the dogs was not deemed clinically important.[13]

Although a reduction in VHS was identified at follow-up in our study, VHS remained above 10.5 in 25.7% of dogs. This finding is consistent with previous studies in which radiographic heart size decreased, but did not always normalize after PDA closure.[1,5,28] Thoracic radiographs are useful for assessing resolution of pulmonary overcirculation and pulmonary edema, but cardiac changes including aneurysmal dilatation of the proximal descending aorta typically persist. In addition, the incidence of acquired HD increases over time, and DMVD, in particular, can contribute to cardiac remodeling despite PDA closure.[29]

In our study, dogs with abnormal LVIDsN and FS values before PDA closure were more likely to have abnormal values at follow-up. FS is affected by loading conditions and values increase when preload is high and afterload is low, physiology typically found with a PDA. After ductal closure, there is an immediate decrease in preload and increase in afterload frequently accompanied by a decrease in FS.[6] An FS <25% was used as a cutoff in this study. Reference ranges for multiple dog breeds, especially larger breeds, can include values as low as 18–20%.[14] At long-term follow-up, median FS was 28%, and 5 of 14 dogs with baseline FS <25% had values between 20 and 25%. Despite evidence of systolic dysfunction, these dogs were clinically doing well, similar to previous studies.[13,28] As with left ventricular dimensions, long-term changes in left ventricular FS can be complicated by residual flow and acquired HD including DMVD.[5]

This study had some limitations in that it was retrospective in nature and encompassed many years over which surgical techniques, interventional catheter-based options, and echocardiographic methods evolved. Baseline echocardiogram images and measurements were often based on M-mode and re-evaluation echocardiograms were done in a similar fashion to have values to compare to initial measurements. The long-term nature of the study allows for an increased incidence of acquired HD, which can confound the results, but is an accurate representation over time. Long-term follow-up evaluations could not be performed in every dog. In general, re-evaluation echocardiograms were more likely to be proactively scheduled for those dogs with complicating issues including systolic dysfunction, residual ductal flow, MR, concurrent congenital or acquired HD, or when receiving cardiac medications. MDD was not significant in statistical analyses, which could be attributed to the fact that MDD measurements were recorded from those obtained with angiography and angiograms were not performed in dogs with surgical ligation. In addition, at the beginning of the study period, after surgical ligation, residual flow and MR were sometimes assessed with auscultation and not echocardiography. FS measurements are influenced by preload and afterload and other echocardiographic methods may provide a more accurate estimate of left ventricular systolic function.[30]

In summary, the results of this study indicate that PDA closure confers an important survival benefit and results in long-term reverse remodeling in the majority of treated dogs. Factors including clinical signs at presentation, concurrent congenital HD, and the presence of severe MR within 24 hours of PDA closure negatively affected survival time. Severe MR after PDA closure is more likely in dogs with left heart enlargement and DMVD. The incidence of acquired HD, specifically DMVD, increases over time as expected, and dogs with LVIDsN above the reference

range and low FS at baseline were more likely to have persistent remodeling at re-evaluations >12 months after PDA closure.

Footnotes

[a] GE Vivid E9; GE Medical Systems, Horton, Norway
[b] Stata MP version 12, 2012, College Station, TX

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