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Right axis deviation in the canine electrocardiogram for predicting severity of pulmonic stenosis: a retrospective cohort analysis

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OBJECTIVE
To investigate the predictive value of right axis deviation of the mean electrical axis (MEA) in assessing the severity of pulmonic stenosis (PS) in dogs.

ANIMALS
Records for 218 client-owned dogs diagnosed between 2014 and 2020 with PS as determined by Doppler echocardiography.

PROCEDURES
University of Florida Small Animal Clinic medical records were reviewed, and signalment and clinical risk variables (murmur grade and clinical signs) were extracted. MEA was determined from ECG records by use of leads I and III. Predictive potential of MEA and associated risk factors to diagnose PS severity (mild [< 50 mm Hg], moderate, or severe [> 75 mm Hg]) were assessed by receiver-operating characteristic curve analysis and quantile regression.

RESULTS
Records for 88 dogs were eligible for analysis. Greater PS severity was associated with smaller breeds presenting with ECG abnormalities, overt clinical signs, and high-category murmur grades (IV and V). Mean MEA increased with stenosis severity category, with an average of 62° for mild, 113° for moderate, and 157° for severe. Each 10° increase in MEA corresponded to an approximately 5–mm Hg increase in PG. Increasing PS severity was associated with MEA right axis deviation > 100° and the more severe cases (PG > 75 mm Hg) with MEA right axis deviation > –180°.

CLINICAL RELEVANCE
Mean electrical axis right axis deviation may be a useful screening metric for dogs with suspected moderate to severe PS.

Pulmonic stenosis (PS) is a common congenital heart defect in dogs, accounting for 31% of total congenital heart defects.[1] Dogs typically present early in life with a left basilar systolic murmur.[2] In patients with advanced disease, right ventricular hypertrophy often manifests as a pronounced right axis deviation (RAD) on ECG.[3] Therefore, RAD may be a useful screening metric for general practitioners both for preliminary diagnosis of PS and determining if referral to a cardiologist is necessary. Although echocardiography is the diagnostic test of choice for PS, it is relatively expensive and not readily available to most general practitioners outside of academic institutions or larger-scale private practices. In contrast, ECG is more accessible to general practitioners and more economical for clients.

The objective of this study was to evaluate the predictive value of deviations from the normal mean electrical axis (MEA) range in a population of dogs already diagnosed with PS of varying severity.

Materials and Methods

Animals

This study involved a single-center retrospective clinical record review conducted at the University of Florida College of Veterinary Medicine (UF-CVM) and approved by the Institutional Animal Care and Use Committee (IACUC No. 202011206). Written owner consent was not required because there was no subject recruitment and data were collected as part of routine clinical management. Records were deidentified but assigned a unique identifier code for analysis.

Records were extracted from UF-CVM's clinical database (Cornerstone Practice Management

Software; Idexx) for 218 dogs diagnosed with PS between May 4, 2014, and September 21, 2020. Records were included if dogs received both an echocardiogram and ECG prior to receiving treatment. Records were excluded if ECGs were missing or unreadable, full echocardiograms were not performed at the University of Florida, dogs were diagnosed with concurrent cardiac abnormalities in addition to PS (eg, Tetralogy of Fallot, subaortic stenosis, tricuspid valve dysplasia, or ventricular septal defect), or dogs received balloon valvuloplasty at other institutions prior to presentation at UF-CVM **(Figure 1)**.

Data collection

Data were extracted by a fourth-year veterinary student and reviewed independently by a board-certified cardiologist. Data recorded were demographic information (breed, age, sex, and reproductive status [entire or neutered/spayed]), body weight (kg), MEA, pressure gradient (PG; mm Hg), murmur grade category (I to VI), clinical signs of stenosis (1 or more of lethargy, ascites, exercise intolerance, collapse, syncope, and congestive heart failure), whether balloon valvuloplasty was recommended or performed at a later date, cardiac medications (atenolol, diuretics, angiotensin-converting enzyme inhibitors, and inodilators), and all-cause mortality for dogs for which death was reported by the owner or referring veterinarian by December 2020.

Clinical procedures

Each dog was evaluated by 1 of 4 board-certified veterinary cardiologists or a resident under supervision of the boarded cardiologist. Murmur grade was determined by the attending cardiologist. Dogs were gently restrained in right and left lateral recumbency without sedation for echocardiography. Pulmonic stenosis pressure gradients (PG; mm Hg) were determined by measuring the peak systolic velocity across the stenotic region with the Vivid E95 (General Electric) or EPIQ 7c (Philips) continuous-wave Doppler echocardiography from the right parasternal short axis and left cranial views.[3–5] Poststenotic dilations were observed from the right parasternal short axis view.[5] Pressure gradient was calculated by use of the modified Bernoulli equation ($PG = 4V^2$, where V = velocity of flow across the stenosis; m/s).[2] The MEA was obtained from ECG leads I and III by use of a 4-lead ECG and calculated by use of established methods.[6] Normal MEA range was defined as 40° to 100°, and right axis deviation (RAD) was defined as MEA > 100°.[6]

Statistical analysis

Descriptive statistics were calculated for 3 PS severity categories: mild (21 to 49 mm Hg), moderate (50 to 75 mm Hg), and severe (> 75 mm Hg).[7] Data were summarized by median and interquartile ranges (IQRs) for nonnormal continuous data and counts (percentages) for categorical data. Because MEA is a circular variable, angular means and SDs were calculated by conversion of MEA to Cartesian vector coordinates (sin and cos transformation).[8] Calculations were performed by use of the SAS macro %circular_moments (SAS Institute Inc).[9] Differences in mean angles between stenosis categories were evaluated by Watson-Williams uniform scores test (W)[8] in R version 4.0.2 (R Foundation for Statistical Computing).

Receiver operating characteristic (ROC) curves were used to predict corresponding MEA based on binary classification of stenosis as either severe or less severe. Stenosis severity categories were defined for 2 PG thresholds (< 50 vs ≥ 50 mm Hg, mild vs moderate-severe; and < 75 vs ≥ 75 mm Hg, mild-moderate vs severe). The 2 models were fitted separately by logistic regression with PROC LOGISTIC (SAS version 9.4; SAS Institute Inc). To assess estimate robustness, optimal MEA cut points were estimated with the SAS macro %rocplot by 3 methods: the maximum proportion of correctly classified observations (CORRECT), the minimum absolute difference between sensitivity and specificity (Sens-Spec = sensitivity – specificity), and the Youden J index (Youden = sensitivity + specificity – 1). The SAS statement PROC PROBIT was used to compute 95% CIs for predicted MEA for each method.

Quantile regression was used to model the relationship of PG in relation to MEA and associated risk factors (age, sex, weight, murmur grade, clinical signs [yes or no], and bulldog [yes or no]) without the dichotomization of PG thresholds required for ROC curve analysis[10] and with relaxation of assumptions required for ordinary least-squares regression.[11] A further advantage of quantile regression is that it allows assessment of differing effects of covariates for dogs at the extremes (and especially the upper tail) of the PG distribution. Predicting high PG is important because higher PG subjects are much more likely to require balloon valvuloplasty. Variable selection was performed

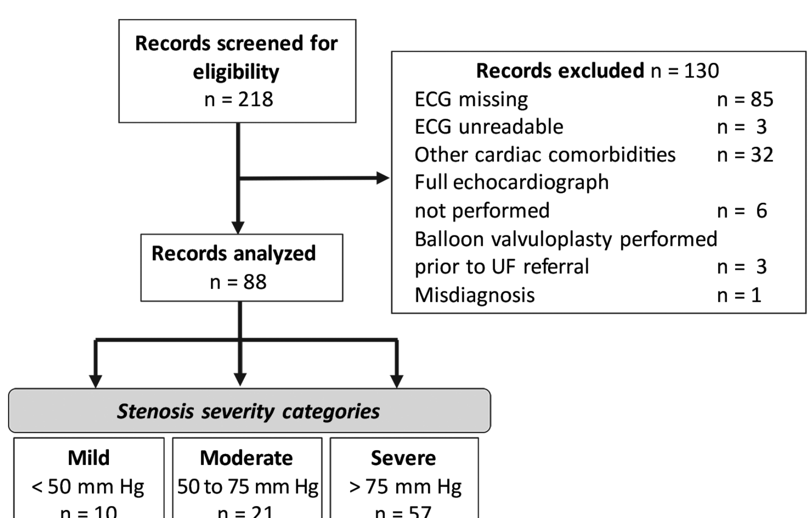

Figure 1—Flow diagram of records screened, excluded, and analyzed in a retrospective chart review of canine pulmonary stenosis. UF = University of Florida.

Table 1—Descriptive statistics for 88 dogs diagnosed with mild (< 50 mm Hg), moderate (50 to 75 mm Hg), or severe (> 75 mm Hg) pulmonary stenosis (PS).

Variable	Mild PS	Moderate PS	Severe PS
No. of males	7	16	29
No. of females	3	5	28
Median (IQR) age (y)	1.6 (0.5–3.0)	0.9 (0.6–2.0)	1.0 (0.5–2.0)
Median (IQR) body weight (kg)	27.2 (10.8–35.0)	17.9 (14.2–24.4)	11.5 (7.2–21.2)
Mean ± SD MEA (°)	62.0 ± 13.1	112.8 ± 50.0	156.8 ± 62.9
No. (%) with all-cause mortality	0 (0)	1 (5)	5 (9)
No. (%) with ECG abnormalities	0 (0)	0 (0)	4 (7)
No. (%) with clinical signs	1 (10)	2 (10)	13 (23)
No. (%) with murmur grade			
II	1 (10)	1 (5)	0 (0)
III	5 (50)	1 (5)	5 (9)
IV	2 (20)	12 (57)	28 (49)
V	2 (20)	7 (33)	14 (42)
No. (%) with medications			
Atenolol	0 (0)	13 (62)	51 (91)
Other	0 (0)	1 (5)	4 (7)
No. (%) with surgery			
Recommended	0 (0)	1 (5)	49 (86)
Performed	0 (0)	3 (14)	42 (74)

IQR = Interquartile (25th to 75th percentile) range. MEA = Mean electrical axis.

with SAS statement PROC QUANTSELECT (SAS Institute Inc) by use of the adaptive lasso method. Final model fit and diagnostics were performed with the SAS statement PROC QUANTREG (SAS Institute Inc), with 90% confidence limits constructed by resampling.[11–13]

Results

Records from 218 dogs diagnosed with PS were screened for eligibility. Records for 88 dogs met the inclusion criteria (Figure 1). With a single exception, all dogs were referred from general practice clinics. Twenty-one breeds were represented, with English and French Bulldogs comprising 26% (23/88) and mixed breeds 32% (28/88) of the sample. Other breeds included pit bull–type breeds (7 [8%]), Cavalier King Charles Spaniel (6 [7%]), Pomeranian (4 [5%]), German Shepherd Dog (3 [3%]), Chihuahua (2 [2%]), Collie (2 [2%]), Yorkshire Terrier (2 [2%]), and 1 each of various other breeds.

Signalment and clinical characteristics were summarized **(Table 1)**. Only 16 of 88 (18%) dogs showed clinical signs associated with PS at presentation. Dogs in the greatest severity category tended to be smaller and were more likely to show ECG abnormalities and overt clinical signs and present with higher murmur grade.

Mean MEA differed statistically between stenosis categories (Watson-Williams W = 29.1; *P* < 0.0001) and increased with stenosis severity **(Figure 2)**, averaging 62°, 113°, and 157° for mild, moderate, and severe stenosis categories, respectively. Mean electrical axis cut points predicted from ROC curve analysis **(Table 2; Figure 3)** varied with the method of optimal cut-point determination, but estimates were clinically consistent within each PG threshold group. Discrimination between mild stenosis (20 to 50 mm Hg) and moderate to severe stenosis (≥ 50 mm Hg) had high concordance (94%) and high sensitivity

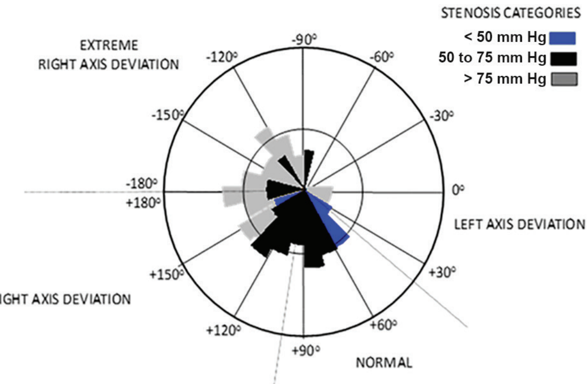

Figure 2—Distribution of mean electrical axis (MEA) readings for 88 dogs diagnosed with pulmonic stenosis and categorized by stenosis severity.

and specificity, and the predicted MEA CI for stenosis < 50 mm Hg showed close approximation to the expected normal range for MEA (40° to 100°). Although setting the stenosis discrimination threshold at a PG of 75 mm Hg resulted in poorer concordance (76%) and lower sensitivity and specificity, the MEA CI was consistent with a right axis deviation > 100°.

A scatterplot was created of PG and MEA with superimposed quantile estimates showing a positive relationship and both increasing variation and slope at higher quantiles **(Figure 4)**. Increasing severity of murmur grade was associated with the largest increases in PG and was largest at the highest percentiles. Quantile regression results are displayed elsewhere **(Supplementary Table S1; Supplementary Figure S1)**. Variables included in the final model were MEA, ln(weight), sex, and murmur grade. Each 10° increase in MEA corresponded to an approximate increase of 5 mm Hg in PG. For each unit increase in body weight (approx 2.7 kg), PG declined by approximately 15 mm Hg, especially in the lower percentiles (< 0.5). Female dogs

Table 2—Receiver operating characteristic curve metrics and predicted MEA (°) for 2 pulmonic stenosis (PS) severity thresholds.

Threshold	Cut-point method	MEA (95% CI)	Sens	Spec	PPV	NPV
Mild vs moderate-severe	Correct, Youden	69 (42–90)	0.949	0.900	0.987	0.692
	Sens-Spec	73 (50–96)	0.897	0.900	0.986	0.529
Mild-moderate vs severe	Correct	101 (48–134)	0.842	0.581	0.787	0.667
	Sens-Spec	126 (90–169)	0.702	0.710	0.816	0.564
	Youden	128 (92–172)	0.684	0.806	0.867	0.581

Optimal cut points for AUC were estimated from maximum number correct (Correct), minimum absolute difference between sensitivity and specificity (Sens-Spec), and Youden's J index (Youden).
Area under the receiver operating characteristic curve was 0.941 (95% CI, 0.908–0.974) for mild (pressure gradient < 50 mm Hg) versus moderate-severe PS (≥ 50 mm Hg) and 0.760 (95% CI, 0.703 to 0.817) for differentiating mild-moderate (< 75 mm Hg) from severe (≥ 75 mm Hg) PS.
NPV = Negative predictive value. PPV = Positive predictive value.

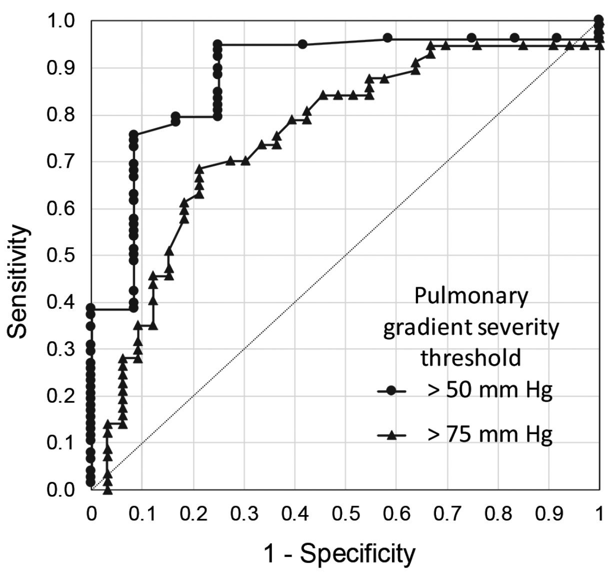

Figure 3—Receiver operating characteristic curves for predicted MEA deviation at 2 pulmonic stenosis severity thresholds: 50 and 75 mm Hg. Predicted MEAs at optimal cut points are given in Table 2.

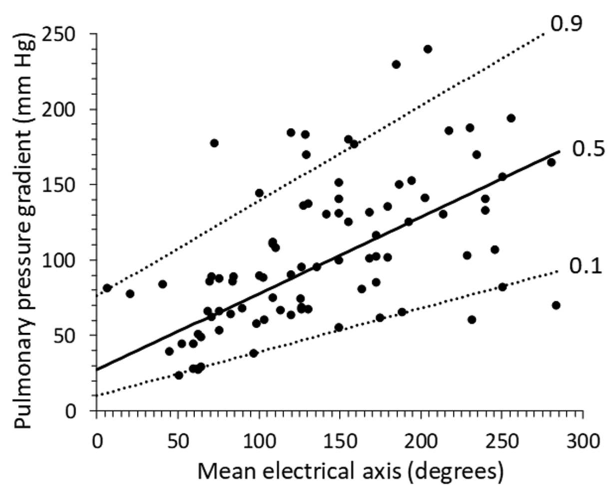

Figure 4—Scatterplot of pulmonary pressure gradient (PG; mm Hg) and MEA (°) for 88 dogs diagnosed with pulmonary stenosis. Quantile estimates at the 10th (0.1) and 90th (0.9) percentiles are indicated by dotted lines and 50th (median, 0.5) estimates by the solid line. Quantile regression coefficients are given in Supplementary Table S1.

showed an increase in PG of approximately 14 to 20 mm Hg over males at the extremes and up to 30 mm Hg in the midrange. A grade IV murmur was associated with an increase in PG of 25 to 40 mm Hg over dogs presenting with murmur grade II to III, and a grade V murmur was associated with an increase in PG of 10 to 77 mm Hg.

Discussion

Secondary effects of PS include right ventricular hypertrophy, ventricular arrhythmias, right-sided heart failure, and abnormal diastolic filling. In patients with moderate and severe PS, MEA RAD is often observed as a result of extensive right ventricular hypertrophy.[3] Because RAD is associated with right ventricular hypertrophy, we predicted that a greater MEA deviation would be associated with greater severity of disease. In the present study, MEA RAD, coupled with smaller body weight and higher-grade murmurs (> III), was shown to be a reasonably good surrogate marker of moderate to severe PS.

Pulmonic stenosis and subsequent severe right ventricular concentric hypertrophy are associated with a 6-fold increase in risk of cardiac death in dogs.[14] However, balloon valvuloplasty decreases the risk of sudden death. In 1 study,[15] 12 of 41 dogs that did not receive balloon valvuloplasty died suddenly, compared with only 1 of 40 dogs that did receive balloon valvuloplasty. Thus, recognition of dogs with severe PS by primary veterinarians is critical to ensure referral to a board-certified cardiologist for therapeutic intervention and an improved outcome. In the present study, overt clinical signs and additional ECG abnormalities, such as arrhythmias, were identified in only a few of the most severely affected dogs, suggesting that these may be relatively late signs. Instead, MEA RAD > 100° was associated with PG > 50 mm Hg and the more severe cases (PG > 75 mm Hg) with MEA RAD > –180°.

Strengths of the present study included a large sample size, the variety of breeds included, and different models for obtaining and evaluating diagnostic predictions. Receiver operating characteristic curves essentially describe a gradient of response (here, stenosis severity) in terms of a dichotomy (eg, mild disease = 0 vs severe disease = 1). However, dichotomization of a response gradient results in considerable loss of both clinical information and power and is strongly discouraged by many applied statisticians.[10] In the present study, similar conclusions were obtained by ROC curve analyses and quantile regression results, namely recognition of increased and clinically actionable PS severity with MEA RAD > 100°. Limitations of this study included the potential for both spectrum and selection bias. Spectrum bias results in variation of diagnostic test performance in different clinical settings because of differences in subject populations and case mix.[16,17] The bias toward more severe stenosis cases at this tertiary referral center limits the generalizability of this study. Dogs with severe PS comprised > 60% of our sample population. However, dogs with louder murmurs and higher pulmonary PG could be more likely to be referred to this center for board-certified cardiology evaluation and therefore may not reflect the clinical range of presentations encountered in general practice. Second, missing or unreadable ECG records resulted in the exclusion of 40% of screened records. This high proportion of loss greatly reduced precision of the models and increased the potential for selection bias. Further investigation with a larger and more representative sample is necessary to accurately determine the predictability of MEA RAD in diagnosing PS severity in dogs.

Clinically, dogs with moderate to severe PS warrant further diagnostic workup including an echocardiogram, serial monitoring, and potential medical or surgical intervention. Additional factors such as breed, age, and murmur characterization coupled with ECG variation will be helpful in the clinical setting to identify more advanced cases of PS. A left basilar systolic murmur should warrant increased suspicion of PS in a young dog, especially in predisposed breeds such as French and English Bulldogs, Chihuahua, Miniature Schnauzer, and American Staffordshire Terrier.[18] In the present study, 94.9% of dogs with moderate to severe PS were correctly identified on the basis of MEA deviation alone. Based on our analysis, an MEA > 100° should increase suspicion of severe PS. In addition, more severe PS was definitely associated with MEA with RAD > –180°. Thus, if a primary care veterinarian suspects PS on the basis of signalment, breed, and murmur characterization and observes an MEA RAD of > –180°, referral to a board-certified cardiologist is strongly recommended.

For general veterinary practices where echocardiography is not available, ECG with evidence of RAD (MEA > 100°) coupled with murmur grade (> III) may be a useful diagnostic for dogs with suspected advanced PS. Identifying and referring cases of severe PS is critical as these patients benefit from early therapeutic intervention.[14] Results from the present study suggested that MEA RAD may be helpful in differentiating severe PS requiring surgical intervention from milder forms of the disease. Thus, ECG with concurrent MEA calculations may be a useful tool during the decision-making process to determine if referral to a board-certified cardiologist for further workup and treatment is warranted.

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org