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Influence of Beta Blockers on Survival in Dogs with Severe Subaortic Stenosis

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Background: Subaortic stenosis (SAS) is one of the most common congenital cardiac defects in dogs. Severe SAS frequently is treated with a beta adrenergic receptor blocker (beta blocker), but this approach largely is empirical.

Objective: To determine the influence of beta blocker treatment on survival time in dogs with severe SAS.

Methods: Retrospective review of medical records of dogs diagnosed with severe, uncomplicated SAS (pressure gradient [PG] ≥80 mmHg) between 1999 and 2011.

Results: Fifty dogs met the inclusion criteria. Twenty-seven dogs were treated with a beta blocker and 23 received no treatment. Median age at diagnosis was significantly greater in the untreated group (1.2 versus 0.6 years, respectively; $P = .03$). Median PG at diagnosis did not differ between the treated and untreated groups (127 versus 121 mmHg, respectively; $P = .2$). Cox proportional hazards regression was used to identify the influence of PG at diagnosis, age at diagnosis, and beta blocker treatment on survival. In the all-cause multivariate mortality analysis, only age at diagnosis ($P = .02$) and PG at diagnosis ($P = .03$) affected survival time. In the cardiac mortality analysis, only PG influenced survival time ($P = .03$). Treatment with a beta blocker did not influence survival time in either the all-cause ($P = .93$) or cardiac-cause ($P = .97$) mortality analyses.

Conclusions: Beta blocker treatment did not influence survival in dogs with severe SAS in our study, and a higher PG at diagnosis was associated with increased risk of death.

Key words: Atenolol; Congenital heart disease.

Subaortic stenosis (SAS) is one of the most commonly diagnosed congenital heart abnormalities of dogs in the United States and Europe[1,2] and is characterized by an abnormal ridge or ring of fibrous tissue below the aortic valve resulting in decreased cross-sectional area of the left ventricular outflow tract (LVOT).[3,4] The prognosis for dogs with SAS is very variable depending on the severity of disease. Severity primarily is classified based upon the pressure gradient (PG) across the stenosis and is divided into 3 categories: mild, moderate, and severe. There is some variability to the classification of SAS. In general, a PG from 16 to 50 mmHg is considered mild, 50 to 80 mmHg is moderate, and a PG ≥80 mmHg is classified as severe.[3,5] Dogs with mild or moderate SAS are considered to have a good prognosis and typically have a normal life span. Treatment for dogs with mild or moderate disease generally is not recommended unless clinical signs develop.[6,7] The prognosis for severely affected dogs traditionally has been considered to be poor based upon a single study evaluating the natural history of SAS that reported a median survival time of 19 months.[3]

Abbreviations:

LVOT	left ventricular outflow tract
PG	pressure gradient
SAS	subaortic stenosis

Empirical treatment with beta blockers commonly is used in the medical management of dogs with severe SAS because of the proposed cardioprotective effects. Beta blockers have negative chronotropic and inotropic effects and are believed to decrease myocardial oxygen demand.[8,9] Atenolol, the beta blocker most commonly used in dogs with SAS, is a selective β-1 receptor antagonist that exerts its effects almost solely on cardiac tissue making it potentially a more attractive choice than less selective beta blockers.[10,11]

Other treatment options for SAS are limited and have included open surgical correction or the use of balloon valvuloplasty.[11–13] Studies that have compared interventional procedures versus beta blocker treatment showed no difference in survival times. However, they did report survival times of approximately 70 months for surgical correction[12] and 55 months for balloon valvuloplasty,[11] survival times that appear considerably longer than the previously reported 19 months for untreated dogs.[3]

Because of the reported poor prognosis in untreated dogs with severe SAS, studies evaluating the use of beta adrenergic receptor blocking drugs against an untreated control group are lacking. Therefore, the

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aim of this retrospective study was to determine if the use of beta blocker treatment affects survival in dogs with severe SAS compared to untreated dogs.

Materials and Methods

Animals

Medical records from the University of Missouri Veterinary Medical Teaching Hospital and the University of Minnesota Veterinary Medical Center were reviewed to identify dogs that were diagnosed with severe SAS between September 1999 and January 2011. Information regarding signalment, age at diagnosis, echocardiographic findings, medications, concurrent disease, development of congestive heart failure, endocarditis or other clinical signs related to heart disease, and date and cause of death when applicable was gathered for each patient. When medical records were incomplete, owners and referring veterinarians were contacted.

Echocardiography

All dogs were diagnosed by or under the supervision of an ACVIM-board certified cardiologist by using standard transthoracic 2-dimensional and Doppler echocardiography without sedation.[14] Three to 5 measurements were averaged for each variable. Peak velocity of blood flow in the LVOT was measured by continuous-wave Doppler and used to calculate a PG using the modified Bernoulli equation ($\Delta P = 4V^2$), where ΔP = PG and V = peak velocity. Dogs with a PG $\geq$80 mmHg were considered severely affected. Dogs with hemodynamically relevant concurrent congenital cardiac disease such as mitral dysplasia, patent ductus arteriosus, pulmonic stenosis, and valvular or supravalvular aortic stenosis causing clinically relevant pressure or volume overload were excluded from analysis. In addition, dogs that underwent a surgical procedure for palliation of SAS or for which there was no follow-up information were excluded. Cardiac death was defined as euthanasia or death after onset of signs of congestive heart failure, or sudden death. Sudden death included witnessed sudden death or discovery of deceased animal with no premonitory signs of illness within the past 24 hours.

Statistical Analysis

All analyses were performed with a commercial statistical software package.[a] Normality was analyzed by using the Shapiro-Wilk test. Baseline descriptive statistics are presented as mean and standard deviation for normally distributed variables whereas nonnormally distributed variables are presented as median and range. Between-group analyses of baseline variables were performed by using unpaired *t*-tests, or the Mann-Whitney rank sum test as appropriate for the data distribution. Time-to-event analyses were carried out in univariate by way of Kaplan-Meier product limit estimates. Cox semiparametric regression models were used to generate multivariate models and adjusted survival curves. Covariates for the multivariate model were presented as both continuous and categorical. Continuous variables were categorized based upon the mean for a given covariate and used in the survival analyses. Model-relative goodness-of-fits were analyzed by Akaike information criterion and compared by using a Chi-Square 1 degree of freedom test. Tests for proportionality were carried out by visual inspection of Schoenfeld residuals, negative log estimated survival distribution function, and formal hypothesis testing of covariates by log (time) interactions followed by Wald Chi-Square statistics and deemed proportional. Additional sensitivity analyses were carried out by using parametric accelerated time failure models affirmatively validating the Cox proportionality assumptions. Fisher's Exact test was used to assess for differences in the proportion of sudden death and congestive heart failure between groups. All analyses were deemed significant at $P < .05$.

Results

Between 1999 and 2011, 50 dogs met the inclusion criteria. The population represented 15 breeds. Golden Retriever (n = 15), Newfoundland (n = 9), Boxer (n = 6), German Shepherd Dog (n = 4), Irish Setter (n = 3), Labrador Retriever (n = 2), Bulldog (n = 2), mixed breed (n = 2), and 1 each: Bull Mastiff, Boston Terrier, English Springer Spaniel, Pug, Rottweiler, Scottish Terrier, and Siberian Husky. Twenty-six dogs were male (9 castrated) and 24 dogs were female (13 spayed).

Twenty-seven dogs received beta blocker treatment. Twenty-three dogs received atenolol at a median dosage of 0.55 mg/kg (range, 0.30–1.2 mg/kg) PO q12h, 1 dog received propranolol at a dosage of 0.64 mg/kg PO q8h, and 1 dog received sotalol at a dosage of 0.9 mg/kg PO q12h. Dosing information was unavailable for 2 additional dogs receiving atenolol. Twenty-three dogs were untreated and served as a comparison group. The median age at diagnosis for the treated group was significantly younger than that of the untreated group (0.6 years [range, 0.2–4.32 years] versus 1.2 years [range, 0.2–11.6 years], respectively; $P = .03$). There was no significant difference in the median PG at diagnosis between the treated and untreated groups (127 mmHg [range, 81–228] versus 121 mmHg [range, 80–217 mmHg], respectively; $P = .20$), or the University of Minnesota and the University of Missouri (116 mmHg [range, 80–190 mmHg] versus 128 mmHg [range, 80–227 mmHg], respectively; $P = .16$). Twenty cases were contributed by the University of Minnesota (treated; n = 1) and 30 cases were contributed by the University of Missouri (treated; n = 26).

No dog had reported episodes of syncope or signs of heart failure at initial presentation. Four dogs in the treated group were diagnosed with mitral valve regurgitation (3 mild, 1 moderate), 1 of which also had mild concurrent tricuspid valve regurgitation, and 2 dogs were diagnosed with mild pulmonic stenosis (PG <25 mmHg). In the untreated group, there was 1 dog with a previously corrected patent ductus arteriosus and 1 dog with mild mitral valve regurgitation.

Mortality Analysis

At time of analyses, 38 dogs (24 in the treatment group and 14 in the untreated group) had died. Ten dogs in the treatment group and 8 dogs in the untreated group were classified as having sudden death. Six dogs in the treatment group died or were euthanized because of heart failure, as were 2 in the untreated group. Ten dogs died of noncardiac-causes (neoplasia, n = 7; and 1 each orthopedic, gastrointestinal, and house fire),

and in 2 dogs the cause of death was undetermined. There was no difference in the proportion of sudden death ($P = .79$) or death because of heart failure ($P = 1.00$) between groups.

The influence of PG at diagnosis, age at diagnosis, and the use of beta blockers on survival was determined by using Cox proportional hazards regression analysis. In all-cause multivariate mortality analysis, only age at diagnosis ($P = .016$) and PG at diagnosis ($P = .025$) influenced survival. The adjusted hazard ratio (AHR) results indicated that as PG at diagnosis increased, there was an associated decrease in survival time (AHR, 1.009; confidence limits [CL], 1.001–1.017; Fig 1). As age at diagnosis increased, there was an associated increase in survival time (AHR, 0.73; CL, 0.56–0.94). Two dogs were censored from cardiac mortality analysis because of inability to determine cause of death. In the cardiac mortality analysis, only PG significantly influenced survival time ($P = .03$; AHR, 1.009; CL, 1.001–1.018).

Treatment with a beta blocker did not influence survival time in the all-cause ($P = .93$; AHR, 1.034; CL, 0.473–2.257; Fig 2) or the cardiac-cause mortality analyses ($P = .97$; AHR, 0984; CL, 0.415–2.333; Fig 3). Median survival time for all-cause mortality was 5.9 years (range, 0.7–11.8 years) in the treated group and 5.1 years (range, 0.8–10.9 years) in the untreated group. Median survival time for cardiac-related mortality was 6.2 years (range, 0.7–11.5 years) in the treated group and 6.7 years (range, 0.8–7.0 years) in the untreated group.

Adjusted survival curves were generated to evaluate the effect of PG at diagnosis on survival in the presence of other covariates in the model. Examination of the AHR plot (Fig 1) indicated the presence of increased hazard at approximately 130 mmHg, thus this was chosen as the division point for analysis. There were 30 dogs with a PG at diagnosis of ≤130 mmHg and 20 dogs with a PG >130 mmHg. In the all-cause mortality analyses, 12 dogs that were still alive were censored (≤130 mmHg, n = 11; >130 mmHg, n = 1). Dogs with a PG at diagnosis of ≤130 mmHg had a median survival of 8.3 years (range, 1.0–11.8 years), whereas dogs with a PG at diagnosis of >130 mmHg had a significantly shorter median survival of 2.8 years (range, 0.7–7.0 years; $P = .03$; Fig 4). In cardiac mortality analyses, 18 dogs were censored from the ≤130 mmHg group, and 5 were censored from the >130 mmHg group. The median survival time for cardiac-related deaths was 11.3 years (range, 1.0–11.8 years) in the <133 mmHg group and 3.0 years (range, 0.7–7.0 years) in the >133 mmHg ($P = .01$).

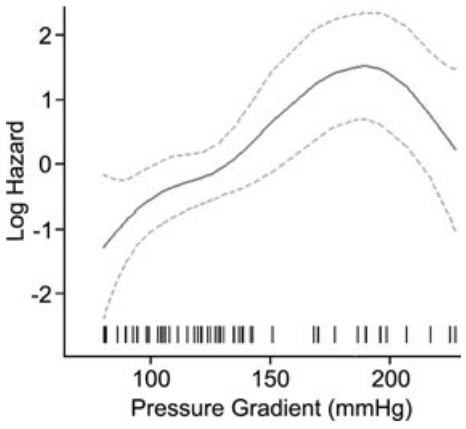

Fig 1. Proportional hazards analyses demonstrating an increased risk of mortality as pressure gradient at diagnosis increases. Pressure gradient (PG) was analyzed as a continuous variable with 4 degrees of freedom for the spline curve. Small vertical lines above the *x*-axis represents the PGs of individual dogs (n = 50).

Discussion

To the authors' knowledge, this is the first study comparing beta blocker treatment in dogs with severe SAS against an untreated group. Beta blocker treatment as used in this study had no demonstrable effect on survival. Only a high PG at diagnosis was associated with a decrease in survival time in both all-cause

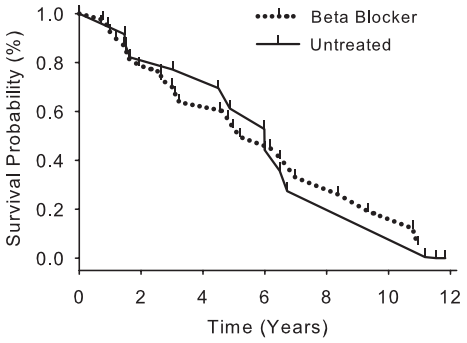

Fig 2. Cox adjusted survival curve of all-cause mortality in dogs with severe subaortic stenosis receiving beta blocker treatment (n = 27) versus untreated (n = 23). There was no significant difference in survival between groups ($P = .93$).

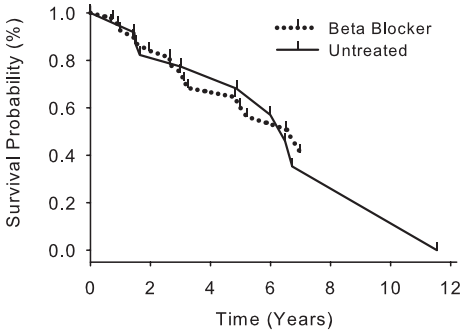

Fig 3. Cox adjusted survival curve of cardiac-related mortality dogs with severe subaortic stenosis receiving beta blocker treatment (n = 27) versus untreated (n = 23). There was no significant difference in survival between groups ($P = .97$).

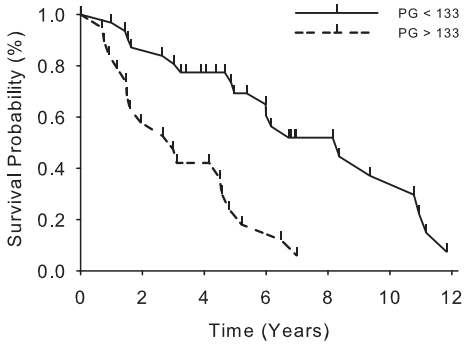

Fig 4. Cox adjusted survival curve of all-cause mortality comparing dogs with severe subaortic stenosis with a PG at diagnosis >130 mmHg (n = 20) and those ≤130 mmHg (n = 30). The division at 130 mmHg was chosen based on the increased hazard occurring at approximately this pressure based on examination of Figure 1. A significant difference in survival between groups was noted ($P = .03$).

and cardiac mortality analyses. The influence of age at diagnosis was significant only in the all-cause mortality analysis. We speculate that early death of dogs with more severe disease may have influenced this result. However, it is also possible that the difference in age between groups was because of chance resulting from a few dogs in the untreated group that were initially diagnosed with SAS at an older age (>8 years, n = 3) versus no dog being >4 years of age at diagnosis in the treated group. Importantly, the results of this study suggest that a greater percentage of dogs with uncomplicated, untreated severe SAS appear to live longer than previously reported.

The mortality analysis strongly suggests that within the severe classification of SAS, PG at diagnosis may be a useful tool in predicting survival time. The data presented in the log hazard graph (Fig 1) showed that an increase in PG in our population was associated with a progressive increase in risk. Although the risk leveled out and decreased starting at approximately 180 mmHg, we believe this was secondary to the relatively small number of dogs at the highest PGs, rather than a true decrease in risk. Only 4 dogs had PG >200 mmHg in this study. A PG >80 mmHg generally has been accepted as severe[3,5]; however, others have noted up to 100 mmHg before clinically relevant complications are expected.[6,15] Redefining mild, moderate, and severe SAS would require additional data and was beyond the scope of this study, but does warrant consideration. Using the median PG of all dogs in our study, we showed that dogs with a PG at diagnosis <133 mmHg have markedly improved median survival times compared to dogs with a PG >133 mmHg (8.3 versus 2.8 years). This has important prognostic value and supports reclassification of what constitutes severe SAS.

The median survival time for all-cause mortality in our untreated group was 61.2 months (5.1 years). Our data suggest that prognosis with severe untreated SAS is better than previously reported,[3] but a normal life span in affected dogs is still unlikely. Nonetheless, comparing results among studies can be problematic. Consideration must be given to the different methods utilized to diagnose SAS (cardiac catheterization versus transthoracic Doppler echocardiography). However, only a small number of dogs in the previous studies were diagnosed by cardiac catheterization, and catheterization has been shown to have excellent correlation with Doppler-derived PGs in SAS.[16,17] In addition, the median age at diagnosis in our untreated group was considerably higher than that of the population reported by Kienle et al[3] (1.2 versus 0.5 years, respectively). The association between age at diagnosis and survival time identified in our study may account, at least in part, for the difference in survival times among the studies. In addition, study size and other unknown characteristics of each study population are potential confounders.

Our study population yielded a total of 50 cases with the majority being large breed dogs. Breeds of dogs in which SAS has been commonly reported include the Newfoundland, Golden Retriever, German Shepherd Dog, Boxer, Rottweiler, and Dogue de Bordeaux.[2,3,15,18,19] In the Golden Retriever and Newfoundland, strong evidence for a genetic basis of SAS has been found, but the exact mode of inheritance does not appear to fit a simple model.[15,18,19] Similar to previous studies, our study population did not show a sex predilection for SAS.[1,2] The high prevalence of Irish Setters (n = 3) within our study population warrants mention because SAS has not previously been reported in this breed. These cases were all from a rescue organization near one of the study institutions (Missouri). Additional investigations would be necessary to determine if Irish Setters are predisposed to SAS in general, or if our results potentially represent a regional founder effect.

Although the characteristics and progression of the disease are strikingly similar in both humans and dogs,[20] a parallel in human medicine to medical management of canine SAS is lacking. Surgical intervention with removal of the fixed obstruction (fibromyectomy) is the treatment of choice in humans with congenital SAS. The timing of the surgery remains a controversial topic because multiple surgeries may be required because of recurrence of stenosis.[20] For valvular aortic stenosis in humans, surgical replacement of the valve is the treatment of choice. No medical treatment has been shown to prolong survival in humans once clinical signs of disease begin[21,22] and beta blocker use is not recommended because of the risk of decreased myocardial function and induction of LV failure.[23] Although no increase in mortality was seen in this study with beta blockade, whether there is a subgroup of dogs at increased risk remains to be shown.

Veterinary surgical or interventional options have not yielded encouraging results and these studies have intentionally excluded a placebo-control group because of the reported short survival time in untreated SAS.[11] Surgical resection of the discrete subvalvular

ridge successfully decreased the PG across the LVOT by 45–65% but failed to show a survival benefit versus treatment with atenolol.[12] Similarly, another study evaluating balloon valvuloplasty for treatment of SAS demonstrated a significant reduction in the PG but failed to show a survival benefit versus atenolol alone.[11] However, similar to our untreated group, survival times for both studies (70 and 55 months, respectively) were longer than previously reported survival times for untreated severe SAS (19 months).[3]

Regardless of treatment, sudden death remains a common outcome in cases of severe SAS[3,11,12] and accounted for 45% of all mortality in this study. The mechanism of sudden death in patients with SAS remains unclear, but abnormalities in myocardial perfusion with resulting ischemia are a potential cause of arrhythmia development. Alterations to the intramural coronary arteries of the left ventricle in dogs with SAS include fibrous intimal proliferation and replacement of medial smooth muscle resulting in a reduction in the lumen of the arteries.[24] Reversal of coronary artery flow during ventricular systole also has been observed in studies of naturally occurring SAS.[25] Experimental models of canine SAS by using aortic banding have demonstrated an increase in myocardial oxygen consumption during exercise suggesting increased vulnerability to ischemic injury compared to normal dogs.[26] Imbalance of myocardial oxygen supply and demand during exercise results in a functional impairment of the subendocardium. Pretreatment with propranolol before exercise appeared to diminish this effect,[8] which suggests that beta blocker treatment may help prevent myocardial ischemia, myocardial dysfunction, or both at least during exercise. However, in our study there were no differences in the proportions of sudden death or heart failure between groups.

Given the retrospective nature of the study, certain limitations must be emphasized. The groups were not randomized and the decision to use beta blocker treatment was solely at the discretion of the clinician managing each individual case. Within the study population, animals evaluated at the University of Missouri were more likely to be treated with a beta blocker than those evaluated at the University of Minnesota. Importantly, however, there was no difference in median PG at diagnosis between the 2 institutions or the 2 treatment groups. In addition, when medical records were incomplete, information gained from direct communication with owners and referring veterinarians was subject to recall bias. The limited follow-up information for some cases made cause of death difficult to determine in those instances. In addition, several dogs within the study were diagnosed with severe SAS before reaching maturity and did not have any further echocardiographic evaluation. It is uncertain what influence this may have had on the subjects' long-term survival. It has been previously shown that SAS can increase in severity over time.[4,20] However, progression does not occur in all dogs, nor is there a predictable increase in severity when it does occur, and in fact, some dogs actually will have a decrease in severity over time.[27] Our wide dosage range, for atenolol also should be considered, and has been previously considered a limitation.[11] However, the median dosage used in this study is consistent with what is commonly recommended clinically.[7] Furthermore, Friedman et al[28] demonstrated that a dosage of 0.7 mg/kg of atenolol in healthy dogs produced a significant decrease in heart rate and cardiac output during exercise compared to control. Adequacy of beta blockade also was tested by injection of a standard dosage of isoproterenol, which failed to cause an increase in heart rate.

Despite these limitations, our results suggest that beta blocker treatment, specifically atenolol at the median dosage used in this study, does not influence survival in dogs with severe SAS. Whether this was because of a lack of efficacy of the drug, a limitation of insufficient dosing, or failure to select appropriate patients is unknown. A prospective, randomized placebo-controlled clinical trial is necessary to confirm or refute these results. Importantly though, the results of this study suggest that dogs with uncomplicated, untreated severe SAS (>80 mmHg) appear to live longer than previously reported. However, a very high PG at diagnosis still confers a poor prognosis for long-term survival.

Footnote

[a] SAS 9.3 (Cary, NC), R v2.15.2, and R Studio v0.97.248

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Conflict of Interest: Authors disclose no conflict of interest.

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