The Natural Clinical History of Canine Congenital Subaortic Stenosis

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The demographics and natural clinical history of canine congenital subaortic stenosis (SAS) were evaluated by retrospective analysis of 195 confirmed cases (1967 to 1991), 96 of which were untreated and available for follow-up evaluation. Of these, 58 dogs had left ventricular outflow systolic pressure gradients available for assessment of severity. All 195 dogs were used for demographic analysis. Breeds found to be at increased relative risk included the Newfoundland (odds ratio, 88.1; $P < .001$), Rottweiler (odds ratio, 19.3; $P < .001$), Boxer (odds ratio, 8.6; $P < .001$), and Golden Retriever (odds ratio, 5.5; $P < .001$). Dogs with mild gradients (16 to 35 mm Hg) and those that developed infective endocarditis or left heart failure were diagnosed at older ages than those with moderate (36 to 80 mm Hg) and severe (>80 mm Hg) gradients. Of 96 untreated dogs, 32 (33.3%) had signs of illness varying from fatigue to syncope; 11 dogs (11.3%) developed infective endocarditis or left heart failure. Exercise intolerance or fatigue was reported in 22 dogs, syncope in 11 dogs, and respiratory signs (cough, dyspnea, tachypnea) in 9 dogs. In addition, 21 dogs (21.9%) died suddenly. Sudden death occurred mainly in the first 3 years of life, primarily but not exclusively, in dogs with severe obstructions (gradient, >80 mm Hg; odds ratio, 16.0; $P < .001$). Infective endocarditis (6.3%) and left heart failure (7.3%) tended to occur later in life and in dogs with mild to moderate obstructions. Left heart failure was uncommon in the absence of additional congenital defects or infective endocarditis. Dogs with mild obstructions lived longer than other groups and tended to remain asymptomatic. The majority of dogs with severe obstructions died before 3 years of age and had a high prevalence (8 of 15) of sudden death. The prognosis for long-term survival in dogs with untreated mild or moderate SAS is favorable (median survival, 30.5 and 51.1 months, respectively), while the prognosis for dogs with severe SAS is very poor (median survival, 18.9 months).

J Vet Intern Med 1994;8:423–431.

Congenital aortic stenosis is an obstructive cardiac malformation reported in the dog,[1-3] cat,[4,5] cow,[6] pig,[7] and human.[8] Although supravalvular, valvular, and dynamic subvalvular forms of aortic stenosis have been recognized, discrete fibromuscular subaortic stenosis (SAS) is the most common form in the dog.[9-14] The lesion usually consists of a ridge, ring, or complex network of fibrous and/or fibromuscular tissue located just below the aortic valve and extending across or encircling the left ventricular outflow tract.[15] Although SAS was previously reported to be the third most commonly diagnosed congenital heart defect in the dog, this defect has been recognized with increasing frequency in the past 5 years, and it is currently ranked first or second in frequency of diagnosis.[1,2,16] Breeds of dogs reported to be predisposed to SAS include the Newfoundland, German Shepherd dog, Boxer, Golden Retriever, and Rottweiler.[16-19] In the Newfoundland, SAS was initially shown to be inherited as a polygenic trait or as an autosomal dominant trait with modifiers, although recently it has been suggested that a single major gene may be involved.[20,21] A heritable basis for SAS is also strongly suspected in other commonly affected breeds.

Dogs with moderate to severe SAS are believed to be at increased risk for sudden death, infective endocarditis, and other complications.[1,12,15,22] However, the magnitude of the risk for these sequelae is not known. As a result, medical therapy (β-adrenergic blockade),[9,10,12,23] surgical therapy (apico-aortic valved conduits,[24] open heart resection,[25] closed heart surgical dilation), or percutaneous transluminal balloon dilation,[1,26] have been advocated. The effectiveness of these treatments has not been determined, in part because of the absence of control groups for comparison. Neither the clinical nor the hemodynamic natural history of untreated SAS in the dog have been reported. Available information regarding clinical course, complications, survival, and causes of death have largely come from anecdotal reports, studies of colony-bred Newfoundland dogs, or relatively small groups of patients.[1,2,20,22]

The objectives of this study were to determine the clinical course of SAS in a group of untreated dogs, to examine the relationship between severity of obstruction and the resulting clinical course, and to develop survival curves for comparative use in evaluating the outcomes of medical or surgical therapy and for advising owners regarding prognosis.

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Accepted January 6, 1994.

Abstract presented at the Ninth ACVIM Forum.

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0891-6640/94/0806-0007$3.00/0

Materials and Methods

The medical records and diagnostic studies of all dogs with suspected or confirmed SAS, diagnosed at the University of California, Davis, Veterinary Medical Teaching Hospital (VMTH) between July 1967 and December 1991, were reviewed. Criteria for a confirmed diagnosis of SAS included (1) direct measurement of a peak-to-peak systolic pressure gradient between the left ventricle (LV) and aorta (Ao) of 15 mm Hg or greater by cardiac catheterization and angiographic demonstration of a subvalvular lesion, (2) a peak LV outflow velocity (V) of 2 m/s or greater by continuous wave Doppler echocardiography (peak systolic pressure gradient estimated by the modified Bernoulli equation, $\Delta P = 4V^2$), with both an increase in peak systolic V $\geq$0.5 m/s between the left ventricular outflow tract and Ao and a turbulent spectral tracing in the proximal aorta by pulsed wave Doppler echocardiography (all Doppler examinations were performed from the left apex with the dogs unsedated), (3) a typical systolic murmur and demonstration of subaortic narrowing and poststenotic dilation of the aorta by two dimensional echocardiography, or (4) gross pathological (necropsy) confirmation of a subaortic fibrous lesion. Of 232 cases initially identified in the computer database, 37 were excluded because of incomplete medical records (n = 12) or inadequate diagnosis (n = 25), leaving 195 confirmed cases of SAS.

Demographic data on the 195 confirmed cases of SAS, including age at initial diagnosis, sex and breed, presenting complaint, severity (pressure gradient), and the presence of additional cardiac abnormalities, were tabulated. Dogs were excluded from the study population if they had other cardiac defects (n = 28), had been treated by surgery (n = 21) or catheter balloon dilation (n = 12), or had been treated for greater than 6 months with propranolol (n = 10). Of the 124 remaining untreated dogs, 28 owners could not be contacted, and these cases were considered lost to follow-up. The remaining 96 untreated dogs were categorized as affected and untreated and were available for follow-up evaluation.

The owners of the 96 untreated dogs were interviewed by telephone and a questionnaire was completed for each case. For surviving dogs, the date of follow-up, prior and current treatments for SAS, clinical signs since discharge, and unrelated medical problems were recorded. For dogs that had died, the date and cause of death (if known), prior treatments for SAS, clinical signs before death, and unrelated illnesses were recorded. For dogs that had been euthanized, it was determined whether euthanasia was chosen because of severe clinical signs related to SAS, an anticipated poor prognosis, or unrelated problems.

The 96 untreated dogs were grouped by clinical outcome into the following categories: (1) alive and asymptomatic, (2) alive and symptomatic, (3) sudden death, (4) death or euthanasia due to complications of SAS, (5) death or euthanasia unrelated to SAS, and (6) euthanasia in an asymptomatic dog shortly after the diagnosis of SAS.

The survival time from birth (age at death or last contact, in months) was determined for all 96 untreated dogs, and the median and range of survival times were calculated and tabulated for each outcome group. For dogs still alive at the end of the study (n = 43), the survival data is censored (these dogs failed to reach the measured outcome, which was death). Using the 58 untreated dogs in which LV-to-Ao systolic pressure gradients were measured, the median and range of systolic gradients were calculated and tabulated for each outcome group. No attempt was made to correct or adjust the gradients based on the method of measurement (ie, Doppler echocardiography versus catheterization). In the 3 dogs in which a gradient was measured by both methods, the average of the two values was used.* Individual gradients were plotted versus survival times for all 58 dogs. Of these, 8 were euthanized at the time of diagnosis, leaving only 50 dogs with both pressure gradients and survival times available for statistical comparison of survival.

To determine whether the untreated dogs (n = 96) were in some way different from those that failed to meet inclusion criteria (n = 99), notched box plots of the age at diagnosis and pressure gradients for each group were examined.[27] Apparent differences were further evaluated using Kruskal-Wallis analysis of variance.[28] Potential differences in breed and sex distribution between the groups was evaluated using Pearson χ^2 analysis of independence.[29]

To evaluate breed and gender as risk factors for the development of SAS, the 5 dominant breeds and their genders, within the 195 confirmed cases of SAS, were compared with the entire population of dogs examined at the VMTH during the same time period. Odds ratios with 95% confidence limits were calculated as estimates of relative risk for these 5 breeds and for male versus female.[30]

The 50 untreated dogs with measured pressure gradients were arbitrarily divided into 3 severity groups. Gradients of 16 to 35 mm Hg were classified as mild, gradients of 36 to 80 mm Hg were classified as moderate, and gradients >80 mm Hg were classified as severe. These gradient ranges were selected primarily to create 3 groups of approximately equal numbers (for statistical purposes) while maintaining realistic ranges of gradient severity. To determine if this arbitrary division of cases produced differences in the age at diagnosis, notched box plots were examined, followed by Kruskal-Wallis analysis of variance. Potential differences in the gender and breed distributions between the groups were evaluated using Pearson χ^2 analysis of independence. Because the dogs that had been euthanized shortly after diagnosis were not used in survival analysis, their gradients were compared with the rest of the untreated group using Kruskal-Wallis one way analysis of variance to determine if these dogs were not randomly excluded with respect to pressure gradient. Also, because SAS has been shown to develop after birth and is believed to worsen during the first year,[19,20] linear regression was performed to determine if a linear relationship existed between the age at diagnosis and the systolic pressure gradient for those diagnoses made during the first year of

* In each of these 3 dogs, the different methods of measurement placed the patient, into the same severity group.

Table 1. The Breed and Sex Distribution of 195 Dogs With SAS

Breed	Male	Female	Total (%)
Newfoundland	17	21	38 (19.5)
Rottweiler	20	14	34 (17.4)
Golden Retriever	17	12	29 (14.9)
German Shepherd Dog	18	2	20 (10.3)
Boxer	13	5	18 (9.2)
Mixed	2	6	8 (4.1)
Samoyed	2	3	5 (2.6)
Bouvier	3	2	5 (2.6)
Mastiff	1	2	3 (1.5)
Pug	2	1	3 (1.5)
Labrador	3	0	3 (1.5)
Shar Pei	2	1	3 (1.5)
6 other breeds (2 ea)*	7	5	12 (6.2)
14 other breeds (1 ea)†	6	8	14 (7.2)
Totals	113	82	195 (100)

* Pit bull, Cocker, Old English Sheepdog, Border Collie, Bernese Mountain Dog, and American Staffordshire Terrier.

† Belgian Sheepdog, Collie, Dachshund, Dalmatian, English Setter, Great Pyrenees, Giant Schnauzer, Hovawart, Alaskan Malamute, Standard Poodle, Wire Haired Fox Terrier, Bull Terrier, Keeshond, English Bulldog.

life.[31] To evaluate severity as a risk factor for sudden death and for the development of clinical signs (including sudden death), odds ratios and 95% confidence limits were calculated as an estimate of relative risk for each severity group.[30]

A Kaplan-Meier survival curve was prepared for 86 untreated dogs (96 untreated dogs minus 10 asymptomatic dogs euthanized at the time of diagnosis).[32] Survival curves were also prepared for each severity group within the 50 dogs with measured pressure gradients and survival times after diagnosis. Differences between groups were analyzed using the Mantel-Cox test of significance between survival curves.[33]

Results

In the 195 confirmed cases, the diagnosis was established by necropsy alone in 10 dogs, by cardiac catheterization alone in 12 dogs, by 2-dimensional echocardiography (2D echo) alone in 45 dogs, and by 2D echo with Doppler echo in 61 dogs. In the remaining 67 dogs, the diagnosis was based on more than 1 of the above procedures (27 necropsies, 57 cardiac catheterizations, 62 2D echoes, and 23 2D and Doppler echoes). The median age at initial diagnosis was 7.0 months (range, 1.4 months to 12.2 years; mean, 18.3 months). Overall, 69% of diagnoses were made in dogs < 12 months of age, and only 19% were made in dogs older than 2 years of age. The breed and gender distributions are shown in Table 1. Of the 195 dogs, 113 (57.9%) were male and 82 (42.1%) were female, with males having 1.4 times increased risk (95% confidence limits, 1.05 to 1.90; $P = .02$). Examination of gender distribution by breed showed that German Shepherd dogs and Boxers accounted for most of this gender difference (Table 1). Thirty-two breeds were represented, with the Newfoundland (19.5%), Rottweiler (17.4%), Golden Retriever (14.9%), German Shepherd dog (10.3%), and Boxer (9.2%) breeds accounting for 71.3% of the total. Of these 5 breeds, all except German Shepherd dogs were found to be at significantly increased risk for the development of SAS (Table 2).

Other cardiovascular abnormalities were present in 28 dogs excluded from evaluation. Of these, 23 dogs had additional congenital defects and 5 had concurrent acquired disorders. The most common congenital defect found in association with SAS was mitral valve dysplasia (n = 12, 6.2%). All but one of these dogs were <1 year of age, and all had moderate to severe mitral regurgitation, moderate to severe left atrial and ventricular dilation, and dysplastic mitral valve features on their echocardiographic and/or necropsy examinations (dogs with mild mitral regurgitation and normal mitral valves were not part of this group). Pulmonic stenosis was present in 7 dogs (3.6%), and patent ductus arteriosus was present in 6 dogs (3.1%). Aortic regurgitation was not considered an additional congenital defect because of its common occurrence secondary to SAS.[34] Two dogs had severe echocardiographic myocardial failure and clinical biventricular failure consistent with acquired dilated cardiomyopathy. Other associated abnormalities are shown in Table 3. In addition, 6 dogs (3.1%, not included in the 28 dogs excluded because of other cardiovascular abnormalities) had concurrent portosystemic shunts with varying degrees of clinical signs.

In comparisons between the untreated group (n = 96) and the excluded" group (n = 99), no differences were observed for median age at diagnosis or breed distribution. The excluded" group had a higher proportion of males and a higher median gradient than the untreated group. Further analysis suggested that dogs with mild SAS (18 to 35 mm Hg) were usually not selected for treatment, while those with moderate

Table 2. Estimated Relative Risks (Odds Ratios) by Breed (n = 195)

Breed	No.	Odds Ratio	95% Confidence Limits	P
Newfoundland	38	88.1	59.7–130	<.001
Rottweiler	34	19.3	13.1–28.5	<.001
Boxer	18	8.6	5.1–14.2	<.001
Golden Retriever	29	5.5	3.64–8.33	<.001
German Shepherd Dog	20	1.3	0.79–2.1	.28

Table 3. Cardiac Abnormalities Associated With SAS (n = 28 Dogs)

Defect(s)	No. of Dogs
MD	7
PS	5
PDA	4
MD and TD	1
MD and mitral stenosis	1
MD and PDA	2
MD and PS	1
PS, TD, and atrial septal defect	1
Eisenmenger's complex	1
Idiopathic dilated cardiomyopathy	2
Heartworm disease with RHF	1
Idiopathic pericardial effusion	1
Left atrial mass with LHF	1

Abbreviations: MD, mitral dysplasia; PS, pulmonic stenosis; PDA, patent ductus arteriosus; TD, tricuspid dysplasia; RHF, right heart failure; LHF, left heart failure.

• One dog with a PDA also had an aberrant left subclavian artery, a left cranial vena cava, and a persistent 4th aortic arch.

to severe SAS (>35 mm Hg) were otherwise randomly distributed between the untreated and treated groups. We concluded that excluding the treated cases from the study (except for demographics) would not affect the validity of the comparisons and conclusions made about the moderate and severe cases.

Of the 96 untreated dogs, 81 (84.4%) were asymptomatic when first examined and were evaluated for the presence of a cardiac murmur. Of the 15 symptomatic dogs, 2 had left heart failure (LHF), 2 had infective endocarditis (IE), 1 had both LHF and IE, 6 had syncope, and 4 had exercise intolerance. At the time of last follow-up contact, 43 dogs (44.8%) were alive and 53 dogs (55.2%) were deceased. Of those deceased, 28 died or were euthanized because of their cardiac disease, 10 were euthanized at the time of diagnosis, and 15 died from unrelated causes. The distribution of outcomes for these 96 dogs, data on age at death or last follow-up, and data on LV-Ao systolic pressure gradients for each outcome group is shown in Tables 4 and 5. Excluding dogs euthanized at the time of diagnosis, the median survival times were 51.1 months for surviving dogs and 17.6 months for nonsurviving dogs ($P = .005$). The median pressure gradient for surviving dogs and deceased dogs (not including those euthanized at the time of diagnosis) was 36.5 mm Hg and 98 mm Hg, respectively ($P = .01$).

Sudden death occurred in 21 (21.8%) of the 96 untreated dogs. Other major complications occurred in 11 additional dogs (11.3%). Of these, 4 had LHF, 3 had IE, 3 had both LHF and IE, and 1 had atrial fibrillation and severe aortic regurgitation. All of these dogs eventually died or were euthanized, 7 because of their cardiac complications and 4 because of unrelated problems. The median gradient of dogs that developed major complications was 45 mm Hg (n = 5; range, 16 to 105 mm Hg), while the median gradient of those that died as a result of the complications was 28 mm Hg (n = 3; range, 16 to 48 mm Hg).

Various combinations of clinical signs (not including sudden death) were reported in 32 (33.3%) of 96 untreated dogs, 10 of which were still living and 22 of which had died, 11 suddenly, 7 of cardiac complications, and 2 of unrelated causes. The remaining 2 dogs were euthanized at the time of diagnosis. Exercise intolerance or fatigue were reported in 22 dogs, syncope was reported in 11 dogs, and respiratory signs were reported (cough, dyspnea, tachypnea) in 9 dogs.

Pressure gradients were obtained in 58 dogs by cardiac catheterization (n = 12), Doppler echocardiography (n = 43), or both (n = 3). Twenty dogs had mild gradients (mean, 26.3 ± 7.2 mm Hg; median, 27.0 mm Hg), 15 dogs had moderate gradients (mean, 50.7 ± 13.5 mm Hg; median, 50.0 mm Hg), and 15 dogs had severe gradients (mean, 113.7 ± 24.1 mm Hg; median, 105.0 mm Hg). There were no significant differences among the 3 severity groups for breed or gender, but there was a significant difference between the groups for age at diagnosis ($P = .032$). Further

Table 4. Survival Times in 96 Dogs With Untreated SAS

		Survival (mo)	
Outcome	No. (%)	Median	Range
Alive	43 (44.8)	51.1	6.8–132
Asymptomatic	33 (34.4)	49.7	6.8–132
Symptomatic	10 (10.4)	68.9	17.8–102
Deceased	53 (55.2)	13.7	2.3–204
Euthanized	10 (10.4)	3.9	2.7–10.1
Sudden death	21 (21.9)	14.4	2.3–105
Complications	7 (7.3)	103	11.8–151
Unrelated	15 (15.6)	21.6	3.9–204

NOTE. Survival is defined as age from birth to death or last follow-up.

Table 5. Pressure Gradients in 58 Dogs With Untreated SAS

		Gradient (mm Hg)	
Outcome No.		Median	Range
Alive	30	36.5	16.0–100
Asymptomatic	24	34.5	16.0–92.0
Symptomatic	6	71.5	50.0–100
Deceased	28	100	16.0–175
Euthanized	8	100	23.0–145
Sudden death	12	103	18.0–175
Complications	3	20	16.0–48
Unrelated	5	36	32.0–144

NOTE. Gradient defined as LV to Ao systolic pressure gradient as measured by Doppler echocardiography or cardiac catheterization.

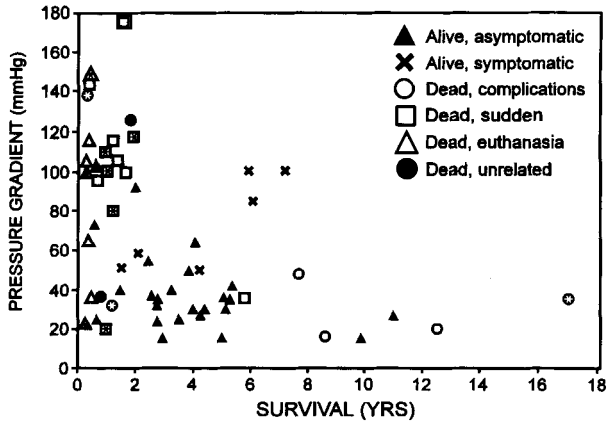

Fig 1. Clinical outcomes and survival times versus systolic pressure gradients for 58 dogs with untreated SAS. *Gradients measured by catheterization.

evaluation showed that the "mild" group was diagnosed at a significantly older age than both the "moderate" group (27.6 versus 6.4 months; $P = .043$) and the severe" group (27.6 versus 6.0 months; $P = .015$). In addition, untreated dogs that eventually died of LHF or IE were diagnosed at a significantly older age than all other untreated dogs (101.0 versus 6.4 months; $P = .002$). In this study, there was no significant difference between median pressure gradients in dogs euthanized at the time of diagnosis compared with other untreated dogs (100 mm Hg with range, 23 to 145 versus 41 mm Hg with range, 16 to 175 mm Hg; $P = .097$), and there was no correlation between the age at diagnosis and the pressure gradient during the first year.

The median LV-Ao pressure gradient in the 58 untreated dogs was 49 mm Hg (range, 16 to 175 mm Hg; mean, 63.4 mm Hg) (Table 5). At follow-up, 30 of these dogs were still alive (6 symptomatic), 12 had died suddenly, 3 died of cardiac complications, 3 died of unrelated causes, and 10 had been euthanized (8 at the time of diagnosis and 2 from unrelated causes). A graph of individual gradients versus survival for these 58 dogs is presented in Fig 1. Assessment of severity as a risk factor for sudden death or the development of clinical signs (including sudden death) showed that patients with severe SAS were 16 times more likely to die suddenly ($P < .001$) and 11.6 times more likely to develop clinical signs ($P < .001$) than the combined mild" and moderate" groups. Patients with mild SAS were 5.2 times more likely to be asymptomatic ($P = .01$) than the combined moderate" and severe" groups. A graph illustrating severity versus outcome is shown in Fig 2.

The survival curve for 86 untreated dogs (96 minus 10 dogs euthanized at the time of diagnosis) is depicted in Fig 3. Separate curves for each severity group (total n = 50) are presented in Fig 4. Median survival time for all 86 dogs was 40.5 months (mean, 49.7; range, 2.3 to 204 months). The median survival time of the severe" group was significantly shorter than the moderate" group (18.9 versus 30.5 months; $P = .003$) and the mild" group (18.9 versus 51.1 months, $P < .001$), while there was no difference between the mild" and moderate" groups ($P = .359$). Median survival times were 14.4, 49.7, 68.9, and 103.6 months for sudden death, asymptomatic, symptomatic, and death due to complications outcome groups, respectively. Sudden death occurred at a significantly younger age than other outcomes ($P < .001$). Although there was a tendency for dogs with LHF or IE to survive longer than dogs without complications, this difference did not reach statistical significance ($P = .078$).

Discussion

The mildest lesions of congenital SAS in dogs are small fibrous nodules located on the ventricular septum just below the aortic valve, while more advanced lesions appear as a distinct ridge, band, or complete ring of fibrous tissue, often involving the base of both the aortic and mitral valves.[19,20] Congenital SAS is often suspected from the detection of a typical basilar systolic ejection murmur in an asymptomatic dog, although fatigue, syncope, sudden death, or left heart failure (LHF) may occur. Electrocardiography and thoracic radiography are rarely diagnostic, and a definitive diagnosis requires echocardiography (especially Doppler echo)[35,36] or cardiac catheterization and angiocardiography. Equivocal or borderline

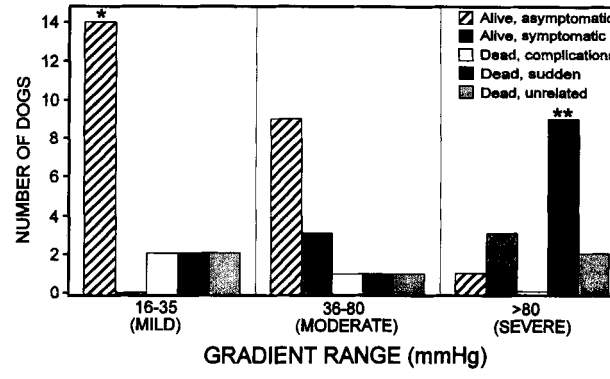

Fig 2. Distribution of outcomes for 50 dogs with SAS and different pressure gradients (dogs euthanized at the time of diagnosis are not shown; see text for details). *Dogs with mild SAS were 5.2 times more likely to be asymptomatic than other groups ($P = .01$); **dogs with severe SAS were 16 times more likely to die suddenly than other groups ($P < .001$).

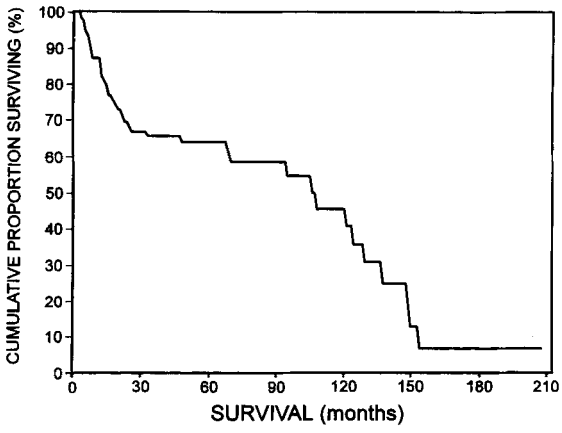

Fig 3. Survival curve for 86 dogs with untreated SAS is depicted as cumulative proportion surviving (%). Survival is from date of birth until date of death or end of study in those dogs still alive. Dogs euthanized at the time of initial diagnosis are not included.

findings can occur in very mild cases. Thus, inclusion criteria for this study were designed to exclude any dogs with equivocal clinical, echocardiographic, or hemodynamic findings.

The mean age at initial diagnosis (18.3 months; median, 7.0 months) and the gender distribution were similar to those of previous reports, except that in our study males were at slightly increased risk, primarily because of the distribution in German Shepherd dogs and Boxers.[2,3,17-19] Most of the dogs in this study were diagnosed before 1 year of age. Of the 19% diagnosed after 2 years of age, about half were presented for LHF and/or IE, and the remainder were diagnosed either as incidental findings at necropsy or when the murmur was detected during examination for an unrelated problem. Dogs with complications were usually diagnosed at an older age, and most had mild gradients. This suggests that dogs with mild gradients may be asymptomatic in early life and survive long enough to develop late complications (usually after 5 years of age).

Buchanan has recently re-examined the breed distribution of SAS and other congenital defects in dogs in the United States, reporting that the Newfoundland, Golden Retriever, Rottweiler, Boxer, and German Shepherd dogs were most commonly affected.[16] The breed distribution and relative risk for SAS in our study was similar to this and previous reports, with two exceptions.[16-19] Since the 1973 report of Mulvihill and Priester,[18] German Shorthaired Pointers have been included in the list of breeds predisposed to SAS. However, no German Shorthaired Pointers were identified among the 195 dogs in our study or in the recent studies of O'Grady[37] and Buchanan.[16] Based on these surveys, we believe that this breed is not predisposed to SAS. There were also more Rottweilers in our population than in previous reports,[18,19,37] resulting in the second highest relative risk (19.3 times) of all breeds. Temporal and geographic differences in breed popularity probably account for these findings, although Buchanan also noted an increased relative risk in this breed.[16] In our hospital population, Newfoundlands had the greatest risk for SAS, as in the studies by Buchanan[16] and O'Grady.[37] Although Golden Retrievers were represented almost as frequently as Newfoundlands, their greater breed popularity accounts for their lower relative risk.

Most dogs with SAS have been reported to be asymptomatic at the time of initial diagnosis,[9-12] a statement supported by this study. The obstruction, especially if moderate to severe, causes LV concentric hypertrophy as well as alterations in coronary arterial blood flow,[38-40] which may lead to the development of clinical signs. Ultimately, ischemia may result in ventricular arrhythmias, or myocardial failure may develop.[20,22] Similar to reports in human patients, fatigue was the most common sign reported in our study, followed by syncope.[41] The average age of symptomatic dogs was higher than in asymptomatic dogs, possibly because of progression of left ventricular hypertrophy and/or myocardial ischemia. Although it has not been independently confirmed, LHF appears to be relatively uncommon, unless SAS is complicated by severe mitral valve or aortic valve regurgitation (either as an associated defect or as a consequence of infective endocarditis).[1,12] In our study, we excluded dogs with pre-existing mitral valve dysplasia, so this factor could not be evaluated. Infective

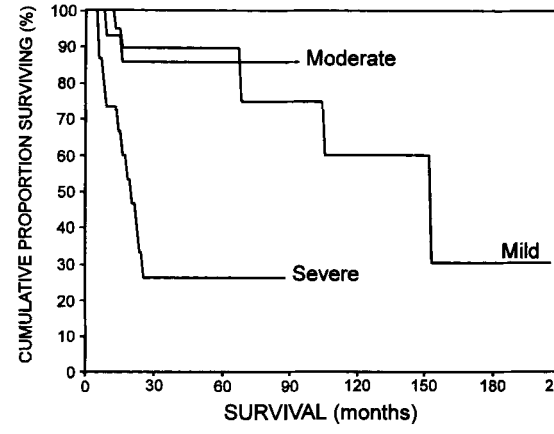

Fig 4. Cumulative survival curves (%) for 50 dogs with SAS, divided into 3 severity groups based on LV-Ao systolic pressure gradients. Survival time of dogs with severe SAS was significantly shorter than dogs with mild ($P = .0005$) or moderate ($P = .003$) SAS. Mild, 15 to 35 mm Hg (n = 20); moderate, 36 to 80 mm Hg (n = 15); severe, >80 mm Hg (n = 15).

endocarditis of the aortic valve may also complicate SAS, causing severe aortic regurgitation and contributing to the development of LHF[22]; this occurred in only 5% of our patients, most of which also had LHF.

Death from LHF at a young age or sudden deaths believed to be caused by myocardial ischemia and ventricular arrhythmias have been reported in dogs.[1,15,20,22] Some dogs with SAS remain asymptomatic until late in life and then succumb to complications or die of unrelated causes.[1,15,20,22] In our study, we identified 21 sudden deaths, 14 unrelated deaths or euthanasias, and 9 deaths or euthanasias associated with late complications. Only 2 early deaths from LHF were found, and both occurred at about 2 years of age. Therefore, early deaths due to LHF appear to be uncommon in dogs with isolated SAS. Sudden death was most common within the first 3 years of life, while major complications, including IE and LHF, tended to occur later in life (after 5 years of age).

Previous reports have suggested that most dogs with SAS and gradients of <50 mm Hg remain asymptomatic and have a normal life expectancy.[9,10,12] Our data support that claim, because the group of dogs still alive at the end of the study and those dying of unrelated causes mostly had systolic gradients < 80 mm Hg. Although the group of dogs still alive at the end of study is a relatively young population, their mean survival has already surpassed that of the group experiencing sudden death, whose gradients were mostly in the severe" range. It has also been reported that dogs with SAS and gradients of 50 to 80 mm Hg have variable clinical signs, whereas those with SAS and gradients > 70 to 80 mm Hg may develop LHF, infective endocarditis, or sudden death.[9,10,12] Our data also supported these statements, except that dogs that developed LHF and/or infective endocarditis generally had mild to moderate gradients. This suggests that dogs with mild to moderate obstructions survived long enough to develop late major complications, whereas dogs with severe obstructions often died suddenly at a young age, before the age when complications tend to develop. In our study population, sudden deaths were common (21.9%), the majority occurring within the first 2 to 3 years. Dogs with severe SAS were 16 times more likely to die suddenly than dogs with mild or moderate SAS. However, 3 dogs that died suddenly had gradients in the mild to moderate range (Fig 2 and 3), indicating that the risk for this outcome is not zero in this group. It should be noted, however, that two of these dogs had gradients determined by catheterization (18 and 80 mm Hg, under general anesthesia) and may have had higher gradients when awake. Also, 3 dogs with gradients in the severe" group (>80 mm Hg) had survived without treatment for 6 to 8 years (Fig 1) by the end of the study (all were symptomatic), indicating that long term survival, although uncommon, is possible in this group.

The Kaplan-Meier curve of the total untreated population revealed two important trends. There was an initial and abrupt death rate in the first 2 to 3 years, mostly due to sudden deaths. The curve was relatively flat from 3 to 8 years, with another increase in deaths occurring in the 8- to 13-year period. This represents unrelated deaths as dogs approached normal life spans, as well as deaths from LHF and IE. The tail of the curve may be somewhat misleading because it represents a single dog with a gradient of 40 mm Hg, which survived to 18 years of age. When comparing the Kaplan-Meier curves between severity groups, the high early mortality in the severe" group is readily seen; this was entirely due to early sudden deaths. There was no difference between the mild" and moderate" groups during the limited follow-up period. Long-term follow up of these groups will be necessary to determine whether this survival trend continues into later years. At least for the first 3 to 4 years of life, however, these survival curves clearly show a high risk for dogs with gradients >80 mm Hg.

Study Limitations

Our data must be interpreted cautiously, considering the limitations of the study. First, there was a selection bias in the study population. As might be anticipated, more dogs with moderate and severe SAS were selected for treatment. Some dogs were euthanized immediately after initial diagnosis, removing them from survival analysis, and there was also a relatively short follow-up period for the most recent cases (almost 50% of the population was diagnosed during the last 4 years of the study period). The increased number of patients diagnosed in the most recent years (a trend supported by other studies[16,37]), especially the mild cases, may have resulted from increased awareness of the disorder by owners of certain susceptible breeds and the availability of Doppler echocardiography to confirm these diagnoses. Also, the strict inclusion criteria may have excluded dogs with very mild or borderline SAS. These factors, plus temporal and geographic effects of breed popularity in our region, undoubtedly influenced our patient population and the resulting breed odds ratios (it is noteworthy that our odds ratios were not markedly different than those determined by Buchanan for a larger group of dogs from multiple institutions).

Second, the use of pressure gradients to classify the

severity of SAS must be understood. Pressure gradients across obstructions are flow-dependent and can vary considerably under different examination conditions, especially if there is a dynamic component to the obstruction. The accuracy of the gradients measured by catheterization and by Doppler echo could have been affected by anesthesia or examination technique, and the validity of combining gradients measured by the 2 methods under different conditions is questionable. Both Doppler- and catheterization-derived pressure gradients may underestimate the true resting pressure gradient, and thereby, the estimated severity of the obstruction. In particular, compared with the awake, resting state, obstructive systolic pressure gradients often decrease by a factor of 30% to 50% under general anesthesia. To justify combining gradients obtained by catheterization alone (n = 8) with those obtained by Doppler alone (n = 39), we determined that 4 of 8 dogs with gradients of 100 mm Hg or greater, as determined by catheterization, were classified as severe" and would have remained in this group regardless of method (none of the 3 other dogs whose gradients were averages of Doppler and catheter values changed categories either). Of the other 4 dogs with gradients determined by catheterization, 1 dog (gradient, 80 mm Hg) probably would have moved from the moderate" to the severe" category, and 3 dogs (gradients of 20, 32, and 35 mm Hg) might have moved from the mild" to the moderate" category (Fig 1). These few changes in categories would not have changed our conclusions and in fact would have strengthened our arguments regarding the poor prognosis in the severe" group and the more favorable prognosis in the mild" and moderate" groups.

Third, some of the data presented here is based on subjective assessment by owners, which is always subject to interpretation. Finally, the small sample size of some outcome groups makes statistical comparisons of these groups less reliable. In particular, the survival curves in Fig 4 were drawn from relatively small numbers of dogs in each group and should therefore be interpreted accordingly.

Conclusions

Despite the limitations noted above, some important conclusions can be drawn from the data. First, sudden death is a common outcome of SAS in the first 3 years of life, especially, but not exclusively, in dogs with severe obstructions; the majority of dogs with gradients >80 mm Hg die before 3 years of age. By contrast, dogs with mild obstructions are at a comparatively low risk for early death. Second, complications such as IE and LHF are rather uncommon and tend to occur later in life and at lower gradients. Third, LHF is uncommon in the absence of other significant congenital defects or infective endocarditis.

Continued follow-up of the large group of dogs diagnosed within the past 4 years should contribute substantial additional data to this study and help determine the validity of our conclusions. Such data will be valuable for evaluating the outcomes of medical and surgical interventions for this common disorder.

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