Survival times in dogs with severe subvalvular aortic stenosis treated with balloon valvuloplasty or atenolol

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Objective—To determine survival times in dogs with severe subvalvular aortic stenosis (SAS) treated by means of balloon valvuloplasty or with atenolol, a β-adrenoceptor blocking drug.

Design—Prospective study.

Animals—38 dogs < 24 months old with severe SAS (peak systolic pressure gradient ≥ 80 mm Hg).

Procedure—10 dogs underwent balloon valvuloplasty and were reexamined 6 weeks later to determine the feasibility of the procedure. The remaining 28 dogs were randomly assigned to undergo balloon valvuloplasty (n = 15) or to be treated with atenolol long term (13) and were reexamined annually for 9 years or until the time of death.

Results—For the first 10 dogs, mean pressure gradient 6 weeks after balloon valvuloplasty (mean ± SD, 119 ± 32.6 mm Hg) was significantly decreased, compared with mean baseline pressure gradient (167 ± 40.1 mm Hg). Median survival time for dogs that underwent balloon valvuloplasty (55 months) was not significantly different from median survival time for dogs treated with atenolol (56 months).

Conclusions and Clinical Relevance—Results suggest that balloon valvuloplasty can result in a significant decrease in the peak systolic pressure gradient in dogs with severe SAS, at least for the short term. No clear benefit in survival times was seen for dogs that underwent balloon valvuloplasty versus dogs that were treated with atenolol. (*J Am Vet Med Assoc* 2005;227:420–424)

Subvalvular aortic stenosis (SAS) is a common developmental disorder in dogs characterized by a subvalvular obstruction, typically a ring or ridge of fibrous or fibromuscular tissue immediately below the aortic valve, that narrows the left ventricular outflow tract.[1-3] Consequences of SAS include left ventricular hypertrophy, intramural coronary arterial sclerosis, myocardial ischemia, and cardiac arrhythmias.[4] The degree of obstruction is typically classified as mild, moderate, or severe on the basis of the magnitude of the peak systolic pressure gradient across the area of stenosis. The prognosis for dogs with mild or moderate obstruction is generally good, with most dogs having near-normal life expectancy. The prognosis for dogs with severe obstruction is generally grave, with most expected to die suddenly or develop bacterial endocarditis or congestive heart failure if they are not treated.[4,5] A median survival time of 19 months has been reported[1] for untreated dogs with severe disease.

Reported treatments for SAS include open surgical correction, balloon catheter dilatation of the subaortic area (balloon valvuloplasty), and administration of β-adrenoceptor blocking drugs.[6-8,a] Although open surgical correction has been shown to reduce the systolic pressure gradient in dogs with severe SAS, it has not been shown to result in significant improvements in survival time.[6,8] On the other hand, to our knowledge, survival times of dogs that have undergone balloon valvuloplasty or that have been treated with β-adrenoceptor blocking drugs long term have not been reported. Thus, the purpose of the study reported here was to determine survival times in dogs with severe SAS treated by means of balloon valvuloplasty or with atenolol, a β-adrenoceptor blocking drug.

Materials and Methods

Animals—Thirty-eight privately owned dogs with severe SAS were included in the study. All dogs were < 24 months old at the time of enrollment in the study. The diagnosis of SAS had been made on the basis of results of 2-dimensional and Doppler echocardiography. Severity of left ventricular outflow tract obstruction was quantified by means of continuous-wave Doppler echocardiography with the transducer placed at the subxiphoid position,[9,10] and in all dogs, peak systolic pressure gradient across the left ventricular outflow tract, determined by means of the simplified Bernoulli equation, was ≥ 80 mm Hg.[9] Dogs with concurrent congenital cardiac abnormalities were excluded from the study, with the exception that dogs with Doppler echocardiographic evidence of aortic or mitral regurgitation were considered eligible for inclusion, as these conditions are commonly associated with SAS in dogs.[1,4]

The first 10 dogs enrolled in the study underwent balloon valvuloplasty to determine the feasibility of the procedure and identify short-term effects of balloon valvuloplasty on the systolic pressure gradient. The remaining 28 dogs were randomly assigned to undergo balloon valvuloplasty or to be treated with atenolol; these dogs were followed up for 9 years or until the time of death to determine the effects of treatment on survival time and rate.

Owners of all dogs included in the study provided written informed consent. The study protocol was approved by The Ohio State University College of Veterinary Medicine Hospital Animal Care and Use Committee.

Balloon valvuloplasty—Balloon valvuloplasty was used to dilate the stenotic subaortic lesion as described.[7] Briefly,

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dogs were anesthetized with halothane or isoflurane, and cardiac catheterization was performed by isolating the right carotid artery. Left ventricular and aortic root pressures were obtained with a high-fidelity, dual-micromanometer, 8-F pigtail catheter or by means of a pull-back procedure with an 8-F pigtail catheter.[b] Catheters were calibrated and pressure recordings were verified by use of a mercury manometer. Pressure transducers were connected to a recorder with 2 pressure amplifiers.[c]

After pressure measurements were obtained, left ventricular and aortic root angiography was performed with dogs in left lateral recumbency by injecting iodinated contrast medium (0.5 mL/kg [0.23 mL/lb]) through a pigtail catheter with a rapid pressure injector. A 200-cm-long, 0.35- or 0.38-mm-diameter, J-tipped guide wire was advanced from the carotid artery into the apex of the left ventricle through the previously placed end-hole catheter. The catheter was removed, and a single high-profile balloon valvuloplasty catheter[d] was passed in retrograde fashion over the guidewire until the radiopaque markers on the catheter were centered over the obstruction. Balloon length was 4 or 5 cm; balloon diameter was chosen by measuring the diameter of the aortic valve annulus on a short-axis, 2-dimensional echocardiographic image of the aorta obtained from the right parasternal position. A balloon with a diameter approximately equal to the diameter of the aortic valve annulus was chosen; in most dogs, a 20- or 23-mm-diameter balloon was used.

The balloon was rapidly inflated by hand with a mixture of contrast agent and saline (0.9% NaCl) solution while the catheter was manipulated by a second individual so that the center of the balloon straddled the stenosis. Inflation was continued until the indentation in the balloon caused by the stenosis had disappeared, maximal balloon inflation had occurred, or the balloon burst. Inflation was maintained for 10 to 20 seconds, and the balloon was then deflated. Two to 6 inflations were performed. Because some balloon catheters were resterilized and reused, inflation was guided by the fluoroscopic appearance of the inflated balloon, as opposed to a specific balloon inflation pressure.

Atenolol administration—Atenolol was available only as 25-mg tablets. Therefore, dosage of atenolol ranged from 0.46 to 1.5 mg/kg (0.21 to 0.68 mg/lb), PO, every 12 hours (mean, 0.85 mg/kg [0.37 mg/lb], PO, q 12 h).

Follow-up evaluation—All dogs were reevaluated by means of Doppler echocardiography 6 weeks after undergoing balloon valvuloplasty or after initiation of atenolol administration. For dogs in the long-term follow-up portion of the study, 2-dimensional and Doppler echocardiography were performed and indirect blood pressure was measured annually. Study end points included development of congestive heart failure, sudden cardiac death, or loss to follow-up. Final follow-up status was obtained by means of telephone conversations with owners of dogs included in the study.

Statistical analyses—Unpaired *t* tests were used to compare peak systolic pressure gradient and age at the time of study enrollment between treatment groups. A paired *t* test was used to compare baseline peak systolic pressure gradient with the gradient recorded during the 6-week follow-up examination. Cumulative survival curves were constructed by means of the Kaplan-Meier method and compared by means of the log-rank test. Survival time was based on date of birth. For purposes of statistical analyses, dogs were censored if they were lost to follow-up, died of noncardiac causes, or were still alive at the conclusion of the study. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

The 10 dogs used to investigate feasibility of balloon valvuloplasty included 4 Golden Retrievers, 3 Newfoundlands, 2 Boxers, and 1 German Shepherd Dog. There were 6 males (5 sexually intact) and 4 females (3 sexually intact). Mean ± SD age at the time of valvuloplasty was 8 ± 4.5 months (range, 4 to 19 months). Mean peak systolic pressure gradient prior to surgery was 167 ± 40.1 mm Hg (range, 116 to 217 mm Hg). Six weeks after balloon valvuloplasty, peak systolic pressure gradient was significantly ($P = 0.009$) decreased (119 ± 32.6 mm Hg; range, 76 to 184 mm Hg), compared with baseline gradient (**Figure 1**).

Of the 28 dogs enrolled in the long-term follow-up portion of the study, 15 were assigned to the balloon valvuloplasty group and 13 were assigned to the atenolol group. Dogs that underwent balloon valvuloplasty included 12 Newfoundlands, 2 Boxers, and 1 Golden Retriever. Nine were male (5 sexually intact), and 6 were female (4 sexually intact). Mean ± SD age at the time of balloon valvuloplasty was 9 ± 4.5 months (range, 5 to 23 months). Mean peak systolic pressure gradient prior to the procedure was 147 ± 43.9 mm Hg (range, 85 to 228 mm Hg). Six weeks after balloon valvuloplasty, peak systolic pressure gradient was significantly ($P < 0.001$) decreased (86.7 ± 36.3 mm Hg; range, 25 to 170 mm Hg).

Dogs treated with atenolol included 8 Newfoundlands, 3 Golden Retrievers, 1 Rottweiler, and 1 Scottish Deerhound. Seven were male (5 sexually intact), and 6 were female (3 sexually intact). Mean ± SD age at the time atenolol treatment was begun was 11 ± 5.5 months (range, 5 to 24 months). Mean peak systolic pressure gradient prior to initiation of atenolol treatment was 122.2 ± 41.0 mm Hg (range, 80 to 215 mm Hg). Mean peak systolic pressure gradient after 6 weeks of atenolol treatment (113.0 ± 46.2 mm Hg; range, 50 to 200 mm Hg) was not significantly ($P = 0.765$) decreased, compared with mean baseline pressure gradient.

Age at the time of study enrollment and baseline peak systolic pressure gradient were not significantly different between dogs that underwent balloon valvuloplasty and dogs treated with atenolol ($P = 0.178$ and 0.136,

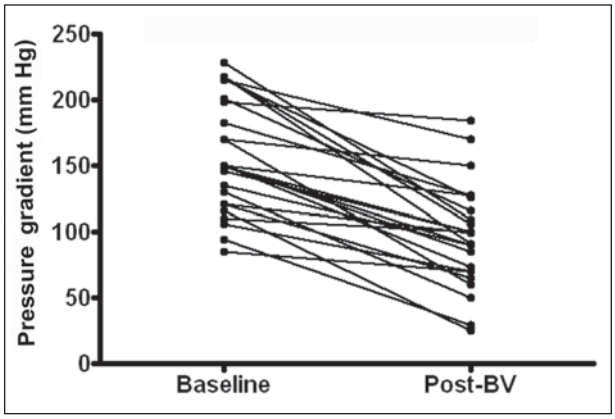

Figure 1—Peak systolic pressure gradient across the left ventricular outflow tract before (baseline) and 6 weeks after (post-BV) balloon valvuloplasty in 25 dogs with severe subvalvular aortic stenosis.

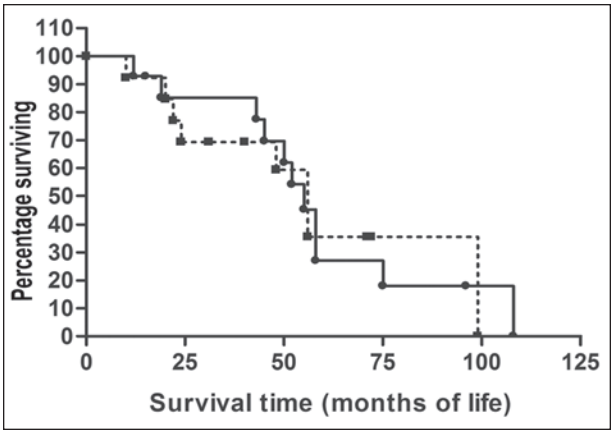

Figure 2—Survival curves for dogs with severe subvalvular aortic stenosis that underwent balloon valvuloplasty (n = 15; solid line) or were treated long term with atenolol, a β-adrenoceptor blocking drug (13; broken line).

respectively). Because of the small number of dogs, breed distribution was not compared between groups.

At the time the study was completed, 21 of 28 (75%) dogs for which long-term follow-up information was available had died. Of the 15 dogs that had undergone balloon valvuloplasty, 9 had died suddenly, 3 had died of congestive heart failure, and 1 had died of endocarditis. The remaining 2 dogs were still alive; these dogs were 52 and 108 months old at the time of the final follow-up evaluation. Of the 13 dogs treated with atenolol, 5 had died suddenly and 3 had died of congestive heart failure. The remaining 5 dogs were still alive; age at the time of the final follow-up evaluation ranged from 40 to 70 months. Median survival time for dogs that underwent balloon valvuloplasty (55 months; range, 12 to 108 months) was not significantly ($P = 0.952$) different from median survival time for dogs treated with atenolol (56 months; range, 10 to 99 months; **Figure 2**).

Discussion

Results of the present study suggest that balloon valvuloplasty can result in a significant decrease in the peak systolic pressure gradient in dogs with severe SAS, at least for the short term. In comparing survival times for dogs that underwent balloon valvuloplasty with times for dogs treated with atenolol, no clear benefit for either treatment was seen. However, the number of dogs included in the study was small.

Because of the poor outcomes previously reported for dogs with severe SAS, we did not include an untreated control group in the present study; all dogs underwent balloon valvuloplasty or were treated with atenolol. Thus, we were unable to determine whether either treatment in the present study resulted in longer survival times than would have occurred without any treatment. Nevertheless, we believe our results should be useful for clinicians who must discuss disease prognosis with dog owners.

The lack of a significant difference in survival time between dogs that underwent balloon valvuloplasty and dogs treated with atenolol was particularly interesting in that one involved daily administration of a generic drug, whereas the other required cardiac catheterization, a procedure associated with substantial cost, specialized equipment, a need for trained operators, and accompanying procedural risks.

Overall survival time for dogs in the present study was seemingly better than that reported in a previous study,[1] in which median survival time for 15 dogs with severe SAS (median peak systolic pressure gradient, 105 mm Hg) that were not treated was 18.9 months. It is tempting to interpret these data as suggesting that balloon valvuloplasty or atenolol administration was beneficial. However, comparison of the outcome of the present study with that of the previous study is problematic for a number of reasons. In the previous study, the diagnosis was made by means of cardiac catheterization or Doppler echocardiography, and pressure gradients measured with each method are slightly different[9] (peak-to-peak pressure gradient with cardiac catheterization and peak instantaneous pressure gradient with Doppler echocardiography). More importantly, anesthesia has a profound effect on the pressure gradient by reducing stroke volume. Accordingly, it is difficult to compare the severity of SAS for dogs in the previous study with severity for dogs in the present study. It is possible that dogs in the previous study were more severely affected than can be determined from the pressure gradients measured by means of cardiac catheterization, and this may have contributed to the shorter survival time. Alternatively, the study populations may have differed in other ways that limit comparison of the results.

Dogs in the present study were all large breeds, and large-breed dogs have typically been suggested to have a higher risk of SAS. Newfoundlands were overrepresented because dogs of this breed were actively recruited to participate. Subvalvular aortic stenosis has been identified in a number of smaller breeds, and whether breed or body size affects survival time or response to treatment in dogs with SAS is unknown. Differences in breed or lesion anatomy also could potentially influence the outcome of balloon valvuloplasty.

Treatment options for dogs with SAS are limited. Open surgical correction with cardiopulmonary bypass has been shown to successfully reduce the systolic pressure gradient in dogs with SAS; however, survival time for treated dogs does not appear to be significantly greater than that for untreated dogs.[8] Balloon valvuloplasty also can decrease left ventricular outflow obstruction, but long-term benefits have not been reported previously. The short-term effects of balloon valvuloplasty on peak systolic pressure gradient appeared evident in the 25 dogs that underwent balloon valvuloplasty in the present study, and results were similar to those reported previously in a study[7] of 9 dogs. Whether peak systolic pressure gradient increases over time in dogs that have undergone balloon valvuloplasty was not addressed in the present study, but this problem has occurred in dogs treated for SAS by means of transventricular dilatation and could affect long-term results.[11] Moreover, the pressure gradient is affected by stroke volume,[12] which was not measured in the present study. An increase in stroke volume consequent to reduction of the obstruction may increase the pressure gradient, so that the benefit of bal-

loon valvuloplasty is underestimated. Conversely, progressive left ventricular systolic dysfunction could reduce stroke volume and lead to overestimation of the benefit of balloon valvuloplasty.

Administration of β-adrenoceptor blocking drugs has been suggested as a potential treatment for SAS because the negative chronotropic and inotropic effects of this class of drugs should reduce myocardial oxygen demand while increasing time for ventricular and coronary filling.[13] The potential for β-adrenoceptor blocking drugs to reduce demand ischemia during exercise or excitement is another possible but unproven additional benefit.[13] Atenolol has been used for patients with heart disease because of its relatively specific effects on heart rate and contractility without strong effects on bronchial and vascular constriction. Although a specific study of drug tolerability was not performed, dosages used in the present study were tolerated for years by the dogs receiving atenolol. One limitation of the present study was the relatively wide dosage range chosen, as it is possible that dosage could also affect outcome.

Sudden death is one of the most common outcomes for dogs with severe SAS,[1] and in the present study, 14 dogs died suddenly. The underlying mechanism for sudden death in dogs with severe SAS is unresolved, but it likely is related to the presence of left ventricular concentric hypertrophy, high wall tension, reversal of coronary blood flow, and arteriosclerosis of intramural coronary arteries.[8,14-17] These changes may lead to development of myocardial ischemia, altered ventricular electrical activity, and lethal ventricular arrhythmias. Whereas β-adrenoceptor blocking drugs do not increase extramural coronary blood flow, except indirectly by prolonging diastole, treatment with these drugs in dogs with experimentally produced aortic stenosis has been shown to decrease ventricular wall stress and impairment of subendocardial blood flow.[18] β-Adrenoceptor blocking drugs may also reduce so-called demand ischemia by limiting myocardial oxygen demand during exercise in dogs with aortic stenosis.[19]

Other mechanisms may also potentially cause sudden death in dogs with SAS. In a study[20] of 9 human patients with aortic stenosis, for instance, ventricular ectopy could not be identified during syncopal attacks, although QRS and ST segment changes were identified. Affected individuals had typical reflex-mediated syncope with a sudden drop in blood pressure, pallor, absent pulses and heart sounds, and loss of consciousness. These findings are characteristic of increases in myocardial contractility mediated by the sympathetic nervous system and associated with an abrupt rise in ventricular pressure and stimulation of myocardial baroreceptors.[21] Sudden death may be a result of diminished coronary flow, reduced heart rate, or altered autonomic state, with eventual development of ventricular fibrillation or asystole.[20,22] Treatment of reflex syncope with β-adrenoceptor blocking drugs could potentially protect the heart by preventing abrupt increases in left ventricular pressure and wall stress that are likely to occur during excitement or exercise. Although density of β-adrenoceptors in the left ventricle may decrease in patients with aortic stenosis, the receptors are functional and capable of stimulation from sympathetic outflow.[23] Although excessive dosages of β-adrenoceptor blocking drugs may reduce cardiac output and could be problematic in patients with untreated congestive heart failure, administration of such drugs is an established treatment for myocardial failure of various causes.[24]

Development of congestive heart failure is a less common outcome for dogs with severe SAS and is believed to be more typically observed later in life.[1] In the present study, 6 dogs developed congestive heart failure.

In conclusion, results of the present study suggest that balloon valvuloplasty can reduce the peak systolic pressure gradient in dogs with severe SAS, at least for the short term. However, there was no clear survival benefit associated with balloon valvuloplasty, compared with long-term administration of atenolol. Both treatments appeared to provide results superior to those published previously for dogs with SAS, but no firm conclusions could be drawn about the benefits of either treatment. The potential value of balloon valvuloplasty in conjunction with long-term administration of a β-adrenoceptor blocking drug should be addressed in future studies.

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