Getting Serious About SAS

Subvalvular aortic stenosis (SAS), the most common congenital heart disease in Golden Retrievers, Newfoundlands and Rottweilers, is a troublesome disease. Known for being highly complex genetically and therapeutically, SAS has a history of taking the lives of seemingly healthy dogs, robbing them of a chance for treatment in their prime.

Part of the problem is that severely affected dogs may not show signs of disease. Additionally, owners may not know or recognize their dogs' decreased exercise ability or the possibility of their fainting or collapsing from excitement. When these dogs die suddenly, their owners are left pondering the cause.

Even for dogs lucky enough to be diagnosed with severe SAS, treatment options that increase quality of life and longevity have been slim. Discovery of the heart defect usually comes after a veterinarian detects a heart murmur, leading to definitive diagnostic testing.

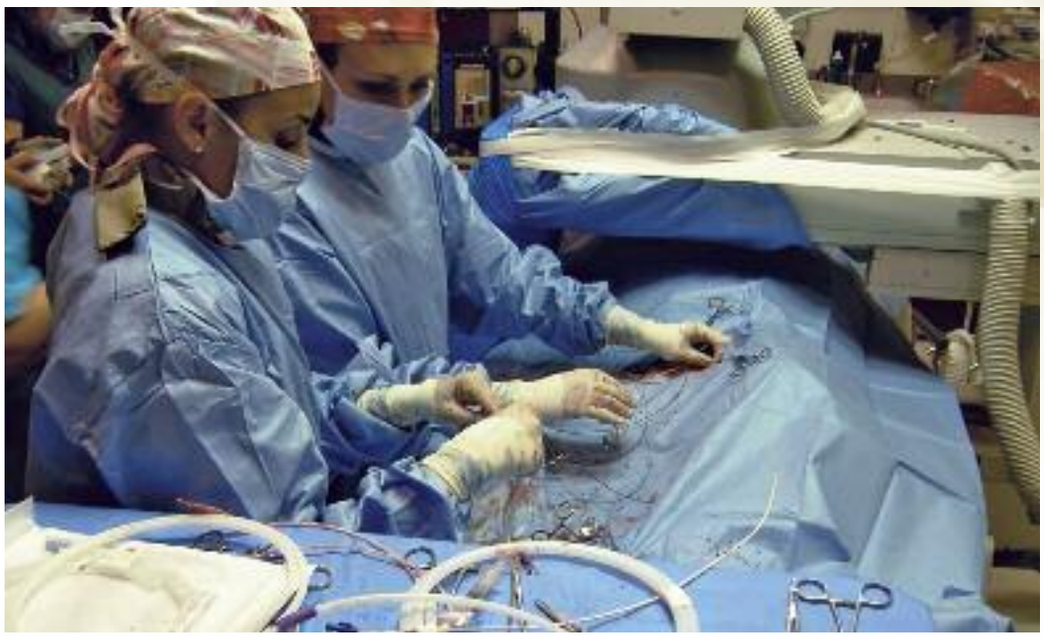
When a dog is diagnosed with SAS — regardless of the severity of disease — breeders receive cautionary advice from experts not to breed the dog. The risk in breeding a dog with SAS is that the heart defect easily can be passed on to offspring regardless of the genetics of the breeding partner.

The dramatic life-shortening potential of severe cases of SAS is reflected in the median 19-month survival for dogs that do not receive treatment. The median survival for dogs receiving medical therapy, consisting of beta blockers to help slow the heart, is 56 months. Dogs with mild to moderate cases of SAS typically live much longer, possibly having normal life spans, although scientific data for life estimates is not available.

Concerns about SAS have prompted the health and education committees of the Golden Retriever, Newfoundland and Rottweiler parent clubs to educate breeders and owners about the disease and to advocate cardiac testing by veterinary cardiologists. All three parent clubs require congenital cardiac testing, along with testing for other health conditions, for dogs to receive their Canine Health Information Center (CHIC) health clearances.

Despite the challenges, good news has come in bits and pieces. Veterinary cardiologists are tackling SAS from a preventive and treatment approach. A novel treatment option being developed and investigated for dogs with SAS is cutting balloon valvuloplasty. This procedure, used for treating coronary artery disease in adults and branch pulmonic stenosis in children, has proved successful in the short term in the majority of dogs with severe SAS that were part of a recent study. The long-term outcome of these dogs continues to be monitored.

Genetic researchers are working to find the causative gene mutation and develop a genetic test. Current research focuses on a region of chromosome 21, where an association appears likely in Rottweilers and Golden Retrievers.



Board-certified veterinary cardiologists Amara Estrada, left, and Mandi Kleman perform cutting balloon valvuloplasty at the University of Florida Veterinary Teaching Hospital on a dog that was part of a study to determine the procedure's effectiveness in treating subvalvular aortic stenosis (SAS). Kleman developed the technique as a veterinary cardiology resident.

Deciphering a Heart Murmur

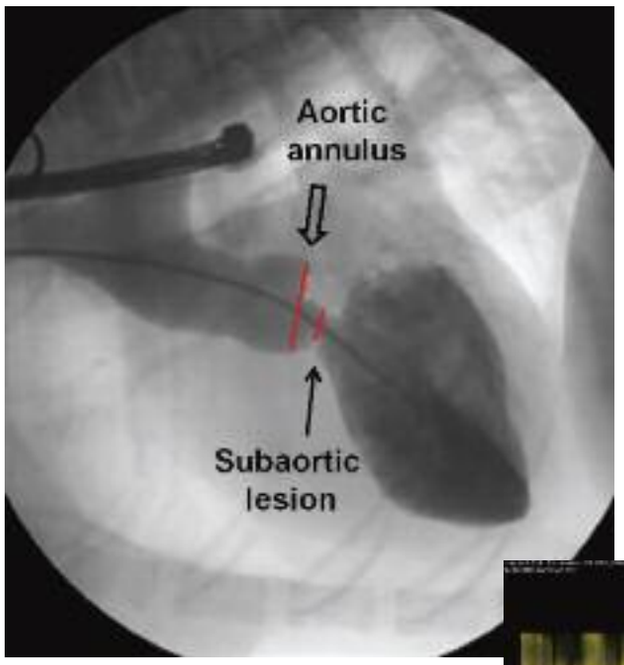
First described in dogs in the 1960s, subvalvular aortic stenosis was not easily diagnosed until basic echocardiography, or ultrasound, began being used in veterinary cardiology in the late 1970s. Two-dimensional echocardiography, which creates an image of the heart, combined with doppler echocardiography, which determines the speed and direction of blood flow, was introduced in the 1980s.

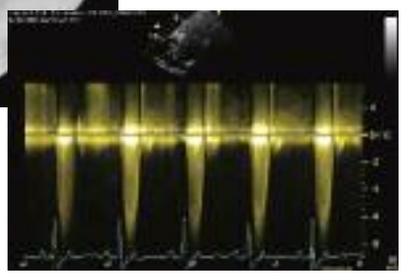
Today, doppler echocardiography is used to view a ring of tissue below the aortic valve that causes the stenosis for which the disease is named. It also detects the turbulent blood flow through the aortic valve that causes the heart murmur. Doppler technology measures the velocity of blood flow and uses this number to estimate the pressure gradient across the lesion, which is critical in making treatment decisions and determining the prognosis for an individual dog.

Even with doppler echocardiography, dogs with uncertain or mild disease can be hard to detect, which is why a board-certified veterinary cardiologist is required to interpret the results of an echocardiogram test for cardiac health clearances. Young puppies could have innocent murmurs not caused by a heart defect that may go away as the heart matures, and athletic dogs may develop physiologic murmurs unrelated to SAS.

A study to determine the cardiac morphological effects of endurance training on Alaskan sled dogs found that the more conditioned the dogs, the higher the incidence of physiologic murmurs.[1] The incidence of heart murmurs was 15.8 percent in unconditioned sled dogs, 27.8 percent in lightly conditioned dogs, and 39.6 percent in highly conditioned sled dogs. The researchers concluded that in sled dogs, as exercise increases, the heart rate decreases, which causes an athletic heart murmur associated with improved athletic performance in dogs subject to regular exercise programs.

The best age to screen for SAS is around 16 weeks, although puppies showing abnormal signs or having a loud murmur should be tested sooner. Though early testing can help identify an affected dog, the Orthopedic Foundation for Animals (OFA) mandates that dogs be 1 year of age prior to ruling them free of SAS. The age requirement relates to SAS being the only congenital heart disease that cannot be ruled out during puppyhood. This problem occurs because the abnormal tissue that causes SAS may begin to develop between 3 and 5 weeks of age but will continue progressing into young adulthood. OFA requires an echocardiogram for dogs with murmurs for cardiac health clearances; however, if a dog does not have a murmur at 1 year of age, the dog can be certified free of SAS by a veterinary cardiologist without an echocardiogram.





Angiography (above) depicts the narrowed stenosis that occurs in dogs with SAS. Inset photo: Doppler echocardiography is used to measure the velocity of blood flow across the stenosis.

Clinical signs of SAS can vary extremely. Besides having a heart murmur, affected dogs may show signs ranging from mild panting and weakness to exercise or heat intolerance. Fainting or collapsing episodes may occur when they are excited or during exercise. Some dogs, even those with severe disease, show no signs.

A veterinary cardiologist is trained to decipher the differences among innocent, athletic and SAS heart murmurs. An echocardiogram is important to diagnose dogs with mild SAS, or soft murmurs, and thus remove them from the breeding pool. Further testing when SAS is suspected may include radiography to evaluate the heart and lungs, basic blood pressure evaluation, and an electrocardiogram to determine heart rhythm, though dogs with SAS often have normal electrocardiogram tests.

The developmental abnormality that occurs in the heart of dogs with SAS causes the secondary clinical signs and problems. The heart is divided into four chambers — the right and left ventricles and the right and left atria. Four valves separate the chambers and ensure that blood flows in one direction through the heart. SAS affects the normal blood flow exiting the heart to the body through the left ventricle via the largest blood vessel in the body, the aorta.

The stenosis, or additional fibromuscular tissue that forms a ridge or ring below the aortic valve, blocks or obstructs the flow of blood through the aorta. The ridge may be small at first but can become progressively more extensive as the puppy grows, causing the opening to the aorta to become narrower. The heart then must work harder during each heartbeat to push the same amount of blood through the narrowed opening. As the blood is forced through the narrow opening, it squirts turbulently at a high velocity, creating the sound of the heart murmur.

Over time, the excessive workload on the left ventricle causes the muscle to thicken and become less flexible, while the space for blood in the chamber becomes smaller. The thickened heart muscle requires more energy and oxygen to work harder and pump an adequate supply of blood to the body. The energy-depleted heart muscle may conduct abnormal electrical impulses that disrupt the normal electrical rhythm of the heart. These arrhythmias may cause exercise intolerance,

fainting spells and are thought to be the cause of sudden death.

Another risk of SAS is bacterial infection of the heart valves, prompting veterinarians to urge owners to look for cuts or breaks in the skin that could lead to infection. Dogs with SAS are put on antibiotics if such an injury occurs, and special care is taken during teeth cleaning and surgical procedures, such as spay and neuter surgeries, where there is potential for bleeding. Congestive heart failure and difficulty breathing are other risks of severe SAS. In contrast, dogs with mild to moderate cases may live normal lives with moderate lifestyle changes.

Beyond Traditional Treatment

The traditional treatment for dogs with SAS has been the use of beta blockers to help slow the heart rate and increase longevity of the dog's life. Slowing down the heart rate helps to decrease the overall workload on the heart muscle by decreasing the heart rate and force of contractions with each beat. Though veterinary cardiologists design treatment programs appropriate for individual dogs, most dogs with severe SAS live on average less than five years even with medical care. Owners of dogs with severe SAS are advised not to let their dogs perform strenuous exercise, as it promotes increased heart work and could complicate abnormal heart rhythms and lead to sudden death.

A low-pressure balloon valvuloplasty was first investigated in dogs with SAS in the early 1990s.[2] In this procedure, a veterinary cardiologist makes a small incision in the neck to thread a long, specialized catheter through the carotid artery into the aorta and across the stenotic region. A balloon on the end of the catheter is then inflated, dilating the stenosis. Unfortunately, survival following this interventional surgery was shown to be similar to dogs treated with beta blockers alone.

More recently, Mandi Kleman, D.V.M., DACVIM-Cardiology, developed a technique using cutting balloon valvuloplasty to help dogs diagnosed with severe SAS. A veterinary cardiology resident at the University of Florida Veterinary Teaching Hospital in Gainesville at the time, Kleman and her mentor, Amara Estrada, D.V.M., DACVIM-Cardiology, associate professor, worked as a team to study the effectiveness of the technique. Funding came from the AKC Canine Health Foundation, the American College of Veterinary Internal Medicine and the University of Florida.

The cutting balloon used in cutting balloon valvuloplasty has four 2-millimeter microsurgical blades that when inflated, left, force open the stenosis causing the heart obstruction. The cutting balloon then is deflated, right, and replaced with a high-pressure balloon that forcibly dilates the stenotic region.

"Based on successful data from children and adults with difficult stenotic lesions, we theorized that cutting balloon valvuloplasty might provide a much-needed new treatment option for dogs with severe SAS," Estrada explains.

In cutting balloon valvuloplasty, the catheter is inserted in the same way as in the traditional low-pressure balloon valvuloplasty. High-technology transesophageal echocardiography and standard angiography allow the surgeon to track the catheter, while it is being threaded into the stenotic region. The cutting balloon is customized with four 2-millimeter microsurgical blades that are about five times sharper than conventional surgical blades.

As the deflated balloon is initially inserted through the carotid artery in the neck, the blades do not touch the arterial walls. When the balloon is inflated, the blades are forced open within the stenotic region, which cuts four incision-like slits into the obstruction. The balloon is then deflated, removed and replaced with a high-pressure balloon, which is inflated to forcibly dilate the stenotic region. The slits created by the blades are opened up with the high-pressure balloon. This combined technique has been evaluated for effectiveness in dilating the tough stenoses in dogs with severe SAS.

"The high-pressure balloon is unique and exciting to evaluate for this purpose," Kleman says. "It is made of Kevlar, the same material used for bullet-proof vests. It achieves very high pressure, which we believe is likely necessary to develop enough force to dilate the very tough fibrous and muscular lesion in SAS."

One of the first dogs to receive cutting balloon valvuloplasty in April 2009 was a Golden Retriever named "Buddy." During a routine veterinary examination when Buddy was 15 months old, the veterinarian exclaimed, "Wow! He has a pronounced heart murmur," recalls Buddy's owner, Cal Ringquist of Inverness, Fla.

Buddy was referred to the University of Florida Veterinary Teaching Hospital in Gainesville, where Kleman was his primary veterinarian on the cardiology team. Though the Golden Retriever did not appear sick, he was considerably underweight. Kleman diagnosed Buddy with severe SAS based on two-dimensional and doppler echocardiography that measured the velocity of his blood across the stenosis. With treatment, Buddy was expected to live maybe three more years.

Although cutting balloon valvuloplasty was a novel surgical procedure, Kleman and Ringquist discussed the limited therapeutic options and decided that it was the right choice for Buddy. Buddy did well during the two-hour surgery and was hospitalized for two days following the procedure to be monitored in the Intensive Care Unit. When he went home, he had a tiny incision on his neck where the surgery took place. He also wore a Holter monitor, essentially a portable 24-hour electrocardiogram, for the first two days to detect any possible irregular heartbeats or arrhythmias

Cal Ringquist and his wife, Marilyn, enjoy quality time with their Golden Retriever, "Buddy," who received cutting balloon valvuloplasty.

following the surgery. The true results of the surgery would be determined soon.

"Before the surgery, Buddy and a Border Collie companion loved to play, but the Border Collie always would outlast Buddy," Ringquist says. "It wasn't long after the surgery until Buddy had more energy than the Border Collie."

The Golden Retriever's health improved in other measurable ways. Over the past two years, Buddy has gained 10 pounds, and his doppler echocardiogram scores have improved. Eighteen months after his surgery, Buddy continued to maintain a 25 percent decrease in the pressure gradient across the SAS lesion, which was estimated from measurements taken from the doppler echocardiography. Though Buddy has a slight heart murmur and must take beta blocker medication and an omega-3 fatty acid supplement for the rest of his life, his heart condition is no longer a daily concern and worry for Ringquist.

"We have deemed Buddy's surgery a success," Kleman says. "The majority, but not all, dogs have had results similar to his. Many of our young patients were noticeably exercise-intolerant prior to the procedure, and it was rewarding to hear of their much-improved energy level and resolution of fainting. Most of our owners have reported their dogs have enjoyed an improved quality of life following the surgery."

The surgery was performed on 14 dogs to determine its effectiveness in treating subvalvular aortic stenosis. The dogs in the study included four Boxers, a French Mastiff, a German Shepherd Dog, six Golden Retrievers, a Rottweiler and a Swiss Mountain Dog.

Kleman will monitor the 11 surviving dogs that were part of the study for the rest of their lives to determine their long-term survival and quality of life. Three dogs died between nine months and 25 months after their surgery due to SAS-related complications, either sudden death or congestive heart failure. Kleman and Estrada caution that the procedure should only be used in dogs with severe cases of SAS, as those with mild to moderate SAS have a reasonably good prognosis.

Presenting the study results last year at the American College of Veterinary Internal Medicine Forum in Anaheim, Calif., Kleman had a success story to share.[3] "Based on these results, we have concluded that cutting balloon valvuloplasty combined with high-pressure balloon valvuloplasty is safe, feasible and effective in significantly decreasing the pressure gradient in dogs with severe SAS," says Kleman, now a clinical cardiologist at Cornell University Veterinary Specialists in Stamford, Conn. "There is potential value in this procedure for canine patients with an otherwise untreatable severe cardiac condition."

Veterinary hospitals around the country are beginning to offer the cutting balloon valvuloplasty. Over the last year, Kleman has provided technical assistance to veterinary cardiologists at Cornell University, the University of California at Davis, The Ohio State University and private referral veterinary hospitals. The patients have been Golden Retrievers, German Shepherd Dogs and one Newfoundland.

The cost may range from $3,000 to $6,000, according to the geographical area and clinic where the surgery is performed. Follow-up care could make the cost even higher. Part of the expense is the highly specialized balloons developed for humans that are not reusable. Estrada and Kleman are optimistic that the cost may be reduced in the future.

Importantly, though SAS is rare in people, this procedure may benefit children with congenital heart disease. Kleman presented her findings last year at the annual meeting of the Pediatric Interventional Cardiology Society, where it was considered a possible treatment option for various conditions.[4]

A Genetic Puzzle

No DNA test exists to determine dogs that carry the gene mutation for SAS or those that are affected or normal. Since the 1970s, researchers have sought the mode of inheritance, and corresponding genetic mutation, but no definitive results have come about.

In the 1970s, researchers at the University of Pennsylvania School of Veterinary Medicine aimed to identify the genetics and pathology of SAS in Newfoundlands. Their study, published in the September 1976 issue of the *American Heart Journal*, determined that SAS was a polygenic disease involving multiple genes.[5] The findings were based on five types of breedings that involved crossing affected and normal Newfoundlands with five non-Newfoundland breeds not affected by SAS (Boxers, Black and Tan Coonhounds, Collies, Labrador Retrievers and Malamutes). The breedings were backcrossed to the affected and normal lines. Ultimately, the researchers suggested that SAS was a dominant trait with various modifying aspects.

Kathryn Meurs, D.V.M., Ph.D., associate dean of research and graduate studies at North Carolina State University College of Veterinary Medicine, has been working on SAS genetic research, along with other canine heart diseases, most of her career. She now believes that SAS may be a recessive genetic disease with variable expression.

Studying the DNA of normal and SAS-affected Golden Retrievers and Rottweilers, she and her colleagues have found a region on chromosome 21 that appears to be associated with the disease in both breeds. "If the gene is responsible for SAS in these two breeds, it increases the likelihood that other breeds with SAS may share the same mutation," Meurs says. "This would mean that development of DNA tests for other breeds would likely be easier even though each breed may have additional genetic modifiers."

Over the past decade, Meurs has been the lead investigator of several research projects supported by the AKC Canine Health Foundation, with funding from the Rottweiler Health Foundation, Medallion Rottweiler Club, Golden Retriever Club of America, Golden Retriever Foundation and the Newfoundland Club of America. The time-consuming collection of pedigrees, DNA samples and clinical information including echocardiography data and physical examinations has contributed to the chromosome 21 finding.

Maryke Nau of Snohomish, Wash., learned about SAS and Meurs' research three years ago, when Meurs worked at Washington State University College of Veterinary Medicine. As the co-breeder of her first litter of Golden Retriever puppies, Nau took the 14-month-old puppies to the veterinary teaching hospital for congenital heart testing for their health clearances. A heart murmur was detected in a female, "Lilly," one of 13 in the litter, which led to a diagnosis of SAS.

"At the time, we thought both parents were clear of SAS," Nau says. "Then, about one and half years ago, an echocardiogram indicated that the dam is affected with SAS. She and Lilly, who recently turned 5 years old, have mild murmurs that do not require treatment."

Little scientific data documents the prevalence of SAS, although the disease is common in Golden Retrievers, Rottweilers and Newfoundlands. It also occurs in Boxers and German Shepherd Dogs. Meurs recommends that breeders do not breed dogs that have SAS. "If a dog merits breeding, it is important to breed to an unrelated dog that does not have SAS and does not have relatives suspected of having SAS," Meurs says.

Despite the challenges, Meurs is optimistic that it is a matter of time before the discovery of a causative gene mutation. Meanwhile, she continues to request blood samples from Goldens, Newfoundlands and Rottweilers that are confirmed to have SAS and that are confirmed clear by echocardiography. Samples should be sent to the Meurs Cardiac Genetics laboratory at North Carolina State University. For information, please contact Meurs at kate_meurs@ncsu.edu or Josh Stern at JSternDVM@gmail.com.

Similarly, Kleman and Estrada are optimistic that combined cutting balloon and high-pressure balloon valvuloplasty will have favorable long-term results for the dogs that underwent the novel surgery. Some of the most severe cases no longer have fainting spells and are more energetic, even though Kleman and Estrada still recommend the dogs should not run.

Reflecting on how the surgery helped his beloved Golden Retriever, Ringquist says, "It saved Buddy's life." ■

Understanding the Severity of SAS

Subvalvular aortic stenosis (SAS) is a potentially fatal congenital heart defect that occurs commonly in Golden Retrievers, Newfoundlands and Rottweilers. Clinical signs vary widely based on the severity of disease. Dogs with mild to moderate SAS may live normal life spans, yet dogs with severe SAS may die suddenly with no signs of disease. Regardless of the severity of SAS, experts recommend that dogs diagnosed with SAS should not be bred. Here is information about the three classifications.

Mild SAS	Doppler echocardiography indicates pressure gradient across the lesion is <40mmHg. A dog usually shows no clinical signs and leads a normal life. Rarely do these dogs develop clinical signs associated with arrhythmias, bacterial valve infections or sudden death.
Moderate SAS	Doppler echocardiography indicates pressure gradient across the lesion from 40mmHg to 80mmHg. A dog may have no clinical signs or may have decreased appetite, reduced exercise capacity, weakness, excessive panting, heat intolerance, fainting or sudden death. These dogs are expected to have a fairly normal life span. Owners are cautioned that dogs may develop clinical signs associated with arrhythmias, congestive heart failure, bacterial valve infections or sudden death.
Severe SAS	Doppler echocardiography indicates pressure gradient across the lesion is >80mmHg. A dog may have no clinical signs or may have decreased appetite, reduced mild to severe exercise capacity, weakness, excessive panting, mild to severe heat intolerance, or mild to severe fainting. Sudden death, often the first clinical sign other than a heart murmur, is common in young dogs. Dogs that do not die suddenly are at high risk as they age for congestive heart failure, bacterial valve infections or sudden death.

Source: Mandi Kleman, D.V.M., DACVIM-Cardiology, Cornell University Veterinary Specialists, Stamford, Conn.

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