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Chapter

Aortic Stenosis in Dogs and Cats: Past, Present and Future

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Abstract

Aortic stenosis is one of the three most common congenital heart defects in dogs and less frequent in cats. Most dogs or cats have subvalvular type of stenosis; valvular or supravalvular types are less frequent. Heart failure is seldom a consequence of aortic stenosis; most dogs with heart failure have a concurrent disease. The most common accompanying diagnosis is pulmonic stenosis, especially in the Boxer breed. Screening programs seem to have efficiently lowered the incidence of aortic stenosis in dogs. Genetic evidence for aortic stenosis has been shown in Golden Retriever, Newfoundland and Dogue de Bordeaux; however, the genetic background of aortic stenosis at molecular level remains unclear.

Keywords: aortic stenosis, congenital heart defect, genetics, sudden death, dog, cat

1. Introduction

Aortic stenosis can be defined as a narrowing of the left ventricular outflow tract (LVOT) and/or aorta at the level below the aortic valve, at the aortic valve, or above it. This narrowing produces a blood flow turbulence that is auscultated as a systolic murmur at the heart base, as well as increased blood flow velocity that can be detected and measured by Doppler echocardiography.

Aortic stenosis is mainly considered to be a congenital defect found in many species including humans. In dogs, aortic stenosis has autosomal inheritance; however, the mode of inheritance seems to be more complex in monogenic traits.

Various forms of aortic stenosis as well as its possible genetic background have been recorded in domestic animals since the late 1960s and 1970s [1]. In those times, the final diagnosis was mostly confirmed at necropsy. Currently, diagnosis is based on echocardiographic evaluation of the morphology of the left ventricular outflow tract and aorta and the velocity of blood measured by the continuous wave (CW) Doppler method after a murmur is detected. Prognosis depends on the severity of the stenosis being from no effect on life quality and expectancy in mild forms of the disease to decreased life quality and expectancy in moderate to severe forms due to possible complications. Those include syncopal episodes that can result in sudden death, tiredness on exertion, or in rare cases, congestive heart failure or infective endocarditis [2].

The aim of this chapter is a review of the existing literature and our experience with clinical aspects of AS in dogs and cats. Genetic evidence for aortic stenosis has been shown in Golden Retriever, Newfoundland, and Dogue de Bordeaux; however, the genetic background of aortic stenosis at a molecular level remains unclear.

2. Forms of aortic stenosis

Subaortic stenosis (SAS) is common congenital cardiac defect in dogs [3, 4] and pigs [5]. In cats, SAS has not been so often described [1, 6–8].

Several classifications are used for aortic stenosis. According to anatomic location, aortic stenosis is classified into valvular (VAS), subvalvular (SAS), or supravalvular (SupAS) [9].

Based on functional characteristics of obstruction, subvalvular cases are further categorized as either fixed (static) or dynamic (labile) [2].

A dynamic form of subaortic stenosis can occur in the following instances: in a hypertrophied left ventricle (LVH) due to protrusion of the ventricular septum into the LVOT, systolic anterior movement of the anterior mitral valve leaflet (SAM) which occurs concurrently or in the absence of LVH, and in cases where aortoseptal angle is smaller than 180° [10].

The subvalvular form—subaortic stenosis (SAS)—has been reported as the most frequently seen (in 95%) and can be presented as a complete or incomplete ring [1, 2, 11–13].

3. Pathologic findings

The gross appearance of the lesions in SAS is variable [4, 14]. Current classification which is used by clinicians is based on anatomical and echocardiographic classification of SAS on the result of postmortem and angiographic studies of Pyle et al. [14, 15]. In a postmortem study performed on Newfoundland puppies, the gross lesions were classified according to severity with grades 1 through 3 [14]. Mild lesions (grade 1) are present as small (1–2 mm), raised white nodules on the endocardium of the ventricular septum below the aortic valve. In some dogs, the nodules are also found on the ventricular surfaces of the aortic valve cusps (**Figure 1**) [14].

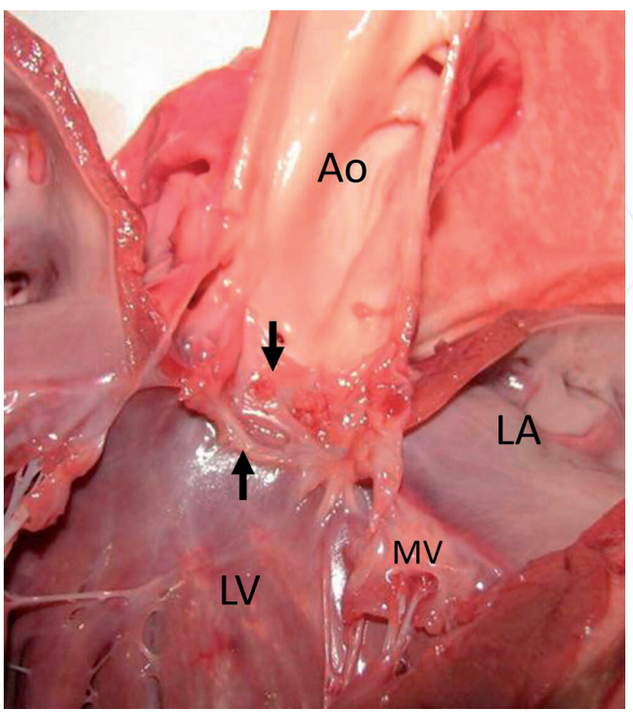


Figure 1.
Gross pathologic specimen from a dog with severe subaortic stenosis. A subvalvular fibrous ring (lower arrow) below the aortic valve and a thickened valve above the fibrous ring of tissue can be seen. Ao—aorta, LV—left ventricle, LA—left atrium, and MV—mitral valve.

Moderate lesions are present as a ridge of endocardial fibrous tissue that in most cases extends from the base of the anterior leaflet of mitral valve across the interventricular septum to beneath the aortic valve (**Figures 2** and **3**) [14]. In severe cases

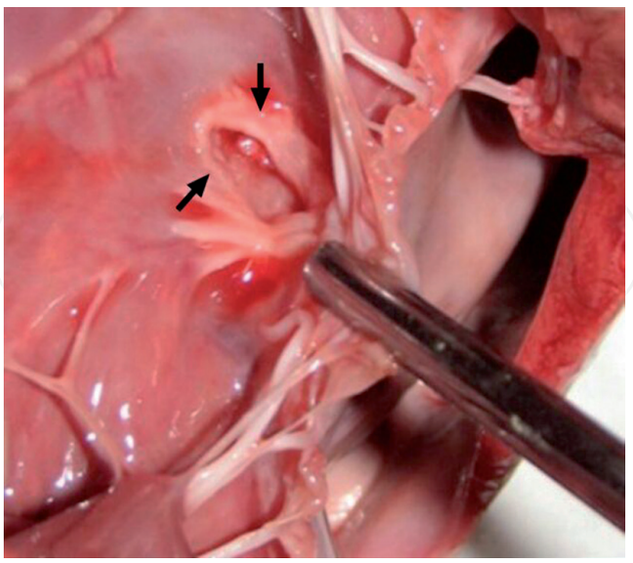


Figure 2.
Gross pathologic specimen from a dog with severe subaortic stenosis. This is a close-up of a closed fibrous subaortic tissue that encircles the left ventricular outflow tract just below the entrance to the aorta.

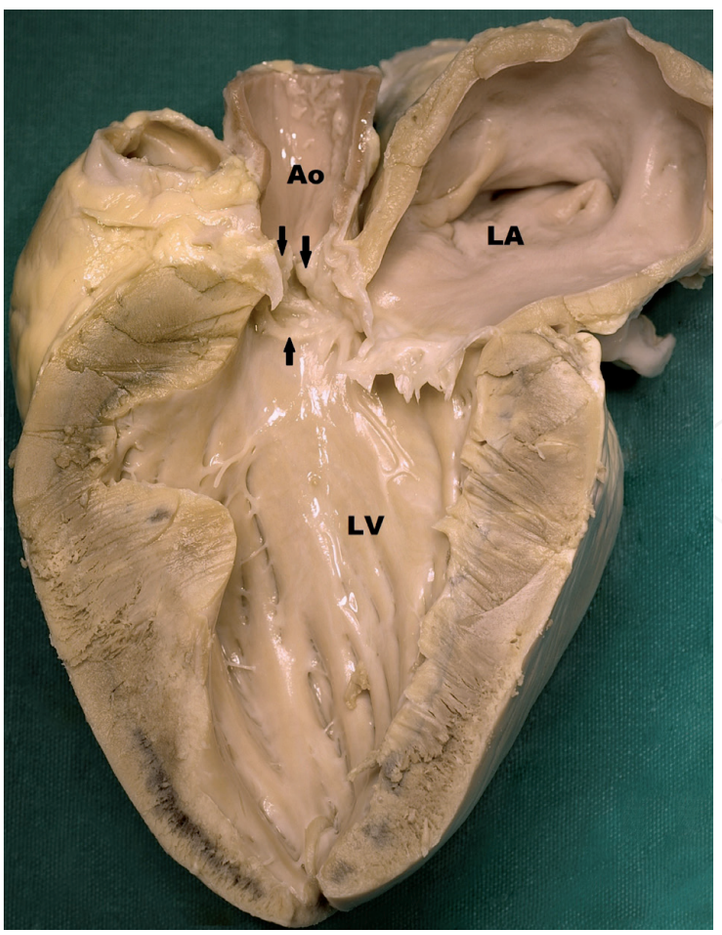


Figure 3.
Gross pathologic specimen from a dog with severe subaortic stenosis. A tunnel-like subaortic stenosis (upper 2 arrows) and a fibrous subaortic ring below the aortic valve is seen (lower arrow). Ao—aorta, LV—left ventricle, and LA—left atrium.

(grade 3), the fibrous band or ridge completely encircles the left ventricular outflow tract below the aortic valve and forms a concentrically narrowing tunnel (**Figure 3**). In most severe cases, anterior leaflet of the mitral valve and ventricular surfaces of the aortic valve are also thickened (**Figure 3**) [14].

Microscopically, the zone of endocardial fibrous tissue below aortic valve contains proliferated mesenchymal cells, mucopolysaccharide ground substance, and foci of metaplastic cartilage [3, 4, 14].

Other cardiac lesions that develop as the consequences of the altered left ventricular outflow include compensatory left ventricular concentric hypertrophy [3] (**Figure 3**) and poststenotic dilatation of the aorta [4].

Microscopic cardiac lesions also include foci of myocardial necrosis, fibrosis in the papillary muscles and subendocardium, thickening of the intramyocardial arteries [3], intimal proliferation of connective tissue, fibrous replacement of smooth muscle in the tunica media [16, 17], and luminal narrowing of intramural coronary arteries [18].

Several cardiac defects have been observed concomitantly with SAS in dogs. These defects include pulmonary artery stenosis (PS), patent ductus arteriosus, mitral valve dysplasia, ventricular septal defect, valvular aortic stenosis, aortic root hypoplasia, persistent left cranial vena cava, bicuspid aorta, quadricuspid aorta, tricuspid dysplasia, double chambered right ventricle, and supravalvular aortic stenosis [19, 20]. Coexistence of aortic stenosis and pulmonary artery stenosis is one of the most common complex cardiac malformations [13, 20].

4. Breed prevalence and natural history

SAS has been ranked the most common congenital heart disease (CHD) in dogs in most European studies accounting for 35% of all CHD. In the United States [12] and in a broad Italian study [20], SAS was on the second place (the most common being PS). However, these results must be taken carefully due to referral population included since a lot of cases were sent for ballooning. Of 4480 dogs included in this study, 976 dogs were diagnosed with congenital heart disease (CHD) of which 21.3% had subaortic stenosis (SAS), while valvular aortic stenosis (AS) was on the fifth place with 5.7% dogs diagnosed. The same study showed many multiple heart defects; the most frequent combination was SAS and PS (26.4%).

We did a study on 9236 dogs, where cardiovascular disease was diagnosed in 6% of dogs, and from those, 12% represented congenital heart diseases of which 45% were aortic stenosis cases [21].

According to many epidemiological studies [20, 22–27], affected breeds are: Boxers, German Shepherd, Newfoundland, Rottweiler, Golden Retriever, Pug, and Bouviers de Flandres. In the Italian study [20] and a Danish study [28], Dogue de Bordeaux was also shown to be significantly affected. German Boxers have proved to be the most sensitive breed in recent years [19, 21, 29–31]. Almost half of all the dogs in the Italian study diagnosed with SAS were Boxers. Boxers are also on top of the list of dogs with pulmonary artery stenosis (PS) and valvular aortic stenosis (AS). In Boxer breed, more male than female dogs are affected with SAS [20, 32]. Studies in cats did not show any breed predilection; aortic stenosis could be of all types described in dogs, with subvalvular stenosis being the most common [6–8, 33]. In our clinic, occasionally a cat with a fixed SAS is detected, usually due to an ausculted murmur. Dynamic left ventricular outflow tract stenosis is much more common in cats due to common occurrence

of hypertrophic cardiomyopathy and systolic anterior motion of the mitral valve (personal unpublished data).

Dogs with mild SAS live longer and mostly remain asymptomatic. Prognosis for the untreated condition in this group is good. Dogs with moderate and severe gradients have shorter life expectancy. They have increased risk of infective endocarditis. The majority of dogs with severe gradients (>80 mm Hg) die before 3 years of age. Median survival was 18.9 months [9, 26].

Subaortic stenosis can be a progressive disease that attains its maximal severity within the first 12–15 months [15]. In dogs that already have high aortic velocity, further progression is unlikely; however, dogs with mild stenosis might progress to a moderate stage [34]. Breeding studies also indicate that AS may not be present at birth but develops during the first 4–8 weeks of life, which suggests that AS is not a true congenital trait but develops postnatally [27].

The etiology of SAS is probably multi-factorial [35]. In the literature, there are two hypotheses on how the fibrocartilaginous ring around the LVOT is formed. It could be derived from embryonal endocardial tissue that retains its proliferative capacity and has chondrogenic potential for some time after birth [14]. A more recent hypothesis suggests that certain anatomic characteristics of the LVOT, including an increased mitral-aortic separation, a decreased aortoseptal angle (AoSA), and a small aortic annulus may cause cellular proliferation in the LVOT because of shear stress caused by abnormal flow patterns [35, 36].

Clinical signs such as weakness, syncope, and sudden death are more commonly seen in dogs with severe or moderate AS than in those with mild SAS [2, 9, 11]. Dogs with mild AS rarely show any signs at all [2, 37]. Careful physical examination reveals crescendo-decrescendo systolic murmur from grades 1 to 6. Final diagnosis has to be confirmed by two-dimensional and Doppler echocardiography, by which evaluation of morphologic characteristics, the type of stenosis, and the pressure gradient across the stenosis can be assessed [2, 11, 15].

Cats are more often identified when clinical signs such as heart failure develop [38].

5. Screening schemes

In the early years of the 21th century, cardiac screening programs have been proposed due to high incidence of some congenital heart diseases. Aortic stenosis has been recognized as one of the most common heart defects according to high prevalence in breeds such as Newfoundland dogs, German Boxer, Golden Retrievers, and Rottweiler to name just the ones mostly affected. Therefore, screening programs were introduced to reduce the high prevalence among the breeding dogs. Some breeders became aware that these breeding programs could help to reduce the incidence of affected animals and to breed healthy puppies. In Italy, such a breeding program helped to reduce the high incidence of AS among boxers [32]. In the case of AS, screening involves careful auscultation to detect cardiac murmur, which is a hallmark of AS. In cases where murmurs are found, 2-D and Doppler echocardiography is carried out, where the morphology of the left ventricular outflow tract with the ascending aorta, specific lesions characteristic for AS/SAS, and increased velocity of the aortic flow can be identified [39].

For a screening program to be effective, a good mutual relationship between the veterinarians involved in screening and pertinent kennel clubs need to be established. Kennel club committees responsible for breeding need to suggest to

breeders to screen their sires and dams before breeding or define the screening as a condition for breeding into their rulebook.

6. Pathophysiology of aortic stenosis

Stenosis across the left ventricular outflow tract into aorta produces a pressure gradient between the left ventricle and aorta, and the gradient is inversely proportional to the degree of the stenotic orifice. The resistance to flow through the stenosis produces a rise of pressure in the left ventricle through the systole; increased wall stress results in concentric hypertrophy of the ventricle. The flow through the narrow passage is like when we squeeze the hose with water – the velocity (v) of the flow will increase proportionally to the narrowing. The relationship between the pressure and the flow is described by a simplified Bernoulli equation:

Pressure gradient (PG) = $4v^2$.

The velocity of the flow or the pressure gradient is used to assess the severity of the stenosis; higher the velocity or pressure gradient, the more severe is the stenosis. However, interpretation of PG must be careful in sedated and excited animals, where there is a change in the resistance and flow [2].

Additionally, the left ventricular wall diameter and cross-sectional area of the aortic orifice are both proportional to the stenosis and can be used to assess the severity [40]. In the hypertrophied ventricle, diastolic filling can be impaired which can cause mild left atrial enlargement.

Turbulent and high velocity flow through the aortic orifice can damage the cusps, and aortic insufficiency can occur consequently. Damaged cusps can predispose to infective endocarditis, as well.

Animals with aortic stenosis can develop heart failure, although this scenario rarely occurs. Myocardial failure could be the one of the reasons for heart failure to develop; however, other complications such as aortic or mitral insufficiency can lead to this kind of progression.

Dogs or cats with aortic stenosis can die suddenly or experience syncopal episodes. The cause might be the reflex peripheral vasodilation on exertion and bradycardia; on the other hand, sudden hypoxia due to exertion or subendocardial fibrosis can predispose to fatal arrhythmias that can also lead to fatal fibrillation [2].

Arterial pulse in patients with aortic stenosis can be reduced in amplitude and can have a delayed systolic peak [2].

7. Diagnostics

To make a diagnosis of AS, a thorough auscultation of heart sounds and murmurs should be carried out. Auscultation is the basic diagnostic technique to uncover AS and every clinically important AS will produce an audible murmur. It needs to be performed carefully in a quiet environment with a dog standing still to be able to hear low intensity murmurs. Although the murmur grade is found to correlate with the severity of AS, it is important to detect also low-grade murmurs to identify dogs with heart defects [41]. Early diagnosis of murmurs due to congenital heart defects may enable early intervention, which may substantially affect long-term outcomes [42]. Many healthy boxers tend to have a soft systolic low-grade murmur; in a study of 201 healthy Boxers, the prevalence of 1–3 grade murmurs was 56%. Boxers with murmurs had higher ejection velocities than boxers without murmurs [43] and young boxers may more commonly have functional murmurs that can also cause mild increase in ejection velocity due to the physiologic changes.

It has been hypothesized that young animals have a larger stroke volume compared to the size of the great vessels than do older animals. This can result in an increase in flow velocity producing turbulence, either in the aorta or in the pulmonary artery, and a resultant innocent heart murmur. The increase in the velocity and associated turbulence is usually mild, so the heart murmur is soft (i.e., grade 1–3/6). The innocent heart murmur generally disappears before 4 to 6 months of age, when the great vessels enlarge in diameter with growth. A notable exception is the Boxer breed, where a smaller left ventricular outflow tract is associated with systolic murmurs in otherwise normal adults [44].

Aortic or subaortic stenosis produces a typical crescendo-decrescendo mid-systolic to holosystolic murmur heard best over the left heart base or also on the right side of the thorax. Loud murmurs tend to radiate peripherally, some can be heard over the carotid artery or over the head. Severe cases of AS have usually harsh, mixed-frequency murmurs of high grade on the scale from 1 to 6 [41]. Murmur intensity significantly correlates with aortic ejection velocity [13, 41, 45]. Identification of low-intensity murmurs correlates with the level of experience. A stress test increased murmur duration and aortic flow velocity [46]. Assessment of the duration of murmur frequency >200 Hz can be used to distinguish physiologic heart murmurs from murmurs caused by mild AS in Boxers and can be used as a complementary method [47].

8. Electrocardiography

Dogs with mild-to-moderate AS usually produce a normal electrocardiogram on the standard ECG recordings, whereas cases with severe AS may show signs of LV hypertrophy in leads II, III, aVF, V2, and V4. Hypertrophied ventricle can be hypoxic; therefore, depression of the ST segment and T wave changes suggest myocardial ischemia or secondary repolarization changes. We may observe ventricular premature complexes in severe cases as well [45]. In cases where AS is combined with other defects, for example, pulmonic stenosis or tricuspid dysplasia, a right axis deviation might occur, depending on the severity of additional lesions. In our study, in boxers with AS/SAS, arrhythmias were observed in 21% of dogs, such as ventricular premature contractions, left bundle branch block and supraventricular tachycardia, atrial fibrillation, atrial premature contractions, sinus bradycardia, and ventricular preexcitation. Dogs with multiple arrhythmias have ussually also heart failure and/or have concurrent malformations [13]. Holter recordings are recommended in symptomatic dogs for detection of possible arrhythmias or S-T segment changes [2].

9. Echocardiography

Echocardiography is the main noninvasive method for diagnosis of aortic stenosis. Two-dimensional mode is used to detect morphologic abnormalities associated with AS/SAS or supravalvular form. In severe cases, LV concentric hypertrophy, subendocardial hyperechogenicity, representing fibrosis (**Figure 4**), and a small subaortic cross-sectional area (**Figure 5**), is found with 2-D echocardiography. Left ventricular hypertrophy, demonstrated by M-mode, has a positive relationship with disease severity [40]. Subaortic fibrous hyperechogenic tissue protruding into the LVOT is seen in the right parasternal or left parasternal long-axis views (**Figure 6** & https://www.vf.uni-lj.si/izobrazevanje/aortic-stenosis-dogs-and-cats-past-present-and-future). In most cases, some aortic valve thickening can be seen

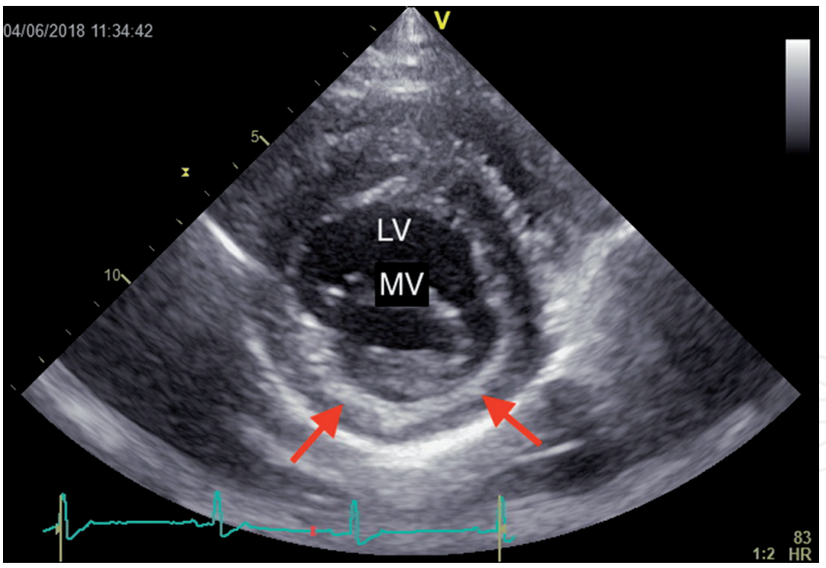


Figure 4.
Two-dimensional echocardiographic image of a short axis of the left ventricle (LV), showing subendocardial fibrosis in the left ventricular free wall. MV—Mitral valve.

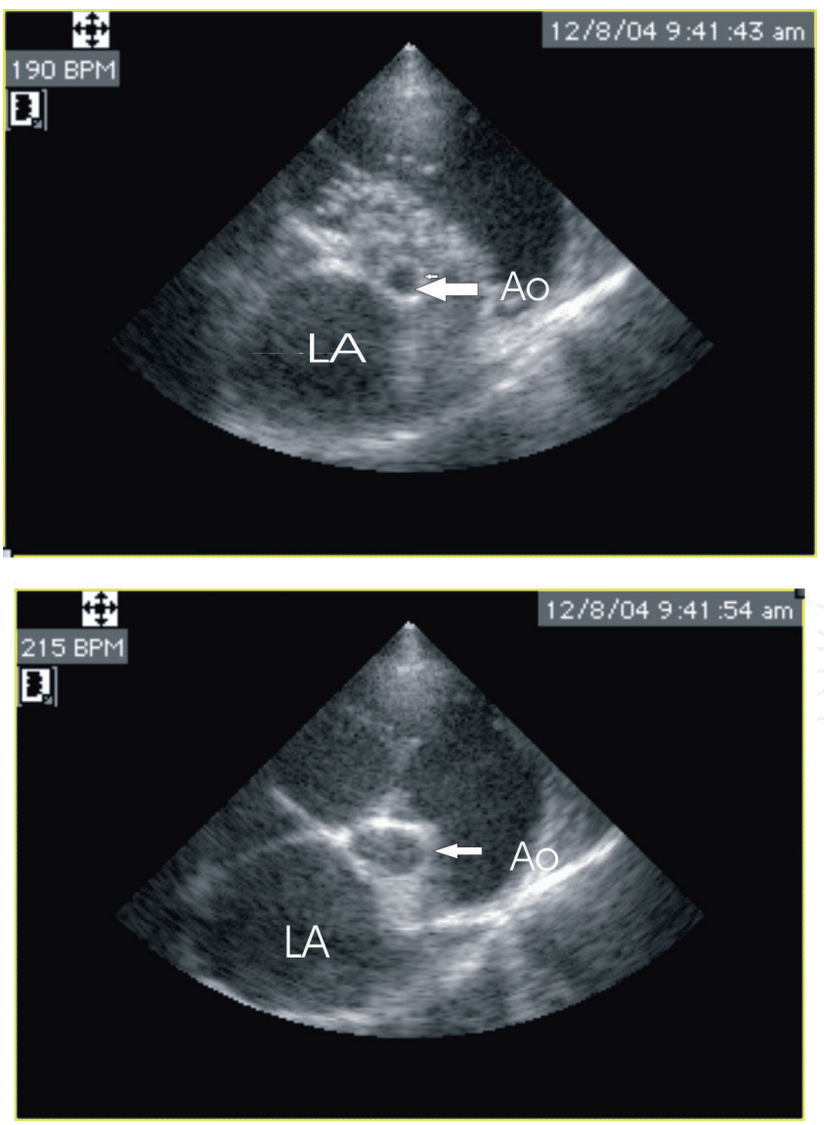


Figure 5.
Two-dimensional echocardiographic image of a short axis at the base of the heart showing subvalvular (upper image) and valvular region (lower image) of the aorta (Ao). One can appreciate the small subvalvular circle compared to the bigger valvular circle. LA—Left atrium.

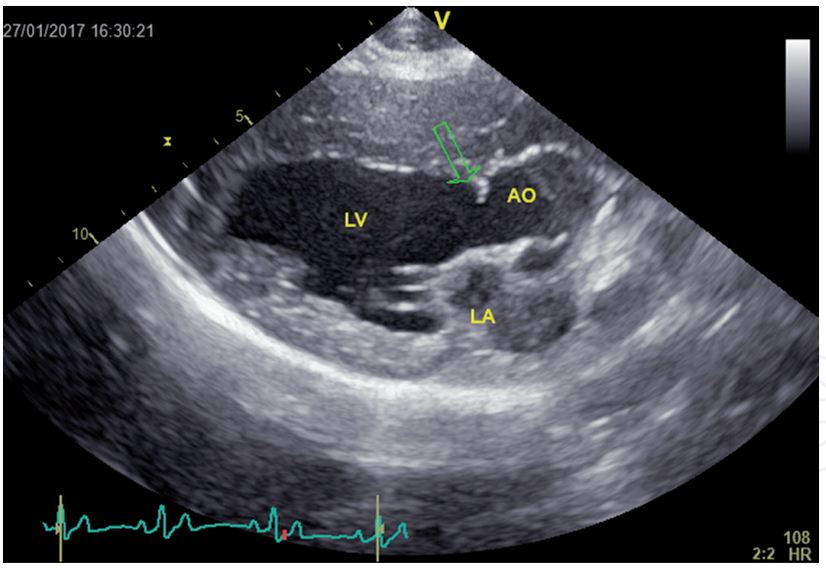


Figure 6.
Subaortic fibrous hyperechogenic tissue protruding into the LVOT is seen in the right parasternal view in a young Newfoundland with severe subaortic stenosis. Ao—aorta, LV—left ventricle, and LA—left atrium.

due to high velocity jets coming to aorta. In cases of true valvular types of stenosis, a poorly moving valve, which does not open completely, can be seen in long-axis (https://www.vf.uni-lj.si/izobrazevanje/aortic-stenosis-dogs-and-cats-past-present-and-future) and cross-sectional views. Color-Doppler mode shows turbulent flow from the obstruction into the aorta (**Figure 7** & https://www.vf.uni-lj.si/izobrazevanje/aortic-stenosis-dogs-and-cats-past-present-and-future). Spectral Doppler modes (continuous Doppler, CW) show high velocity jet, often accompanied with aortic regurgitation (**Figure 8**, https://www.vf.uni-lj.si/izobrazevanje/aortic-stenosis-dogs-and-cats-past-present-and-future). Subcostal transducer placement proved to be superior to the left ventricular apical and the suprasternal view to detect the highest velocity through the aortic orifice [48]. Normal velocities through the aorta differ among breeds and studies; however, the average velocity does not exceed 1.8 m/s from the left apical view or 2 m/s from the subcostal view

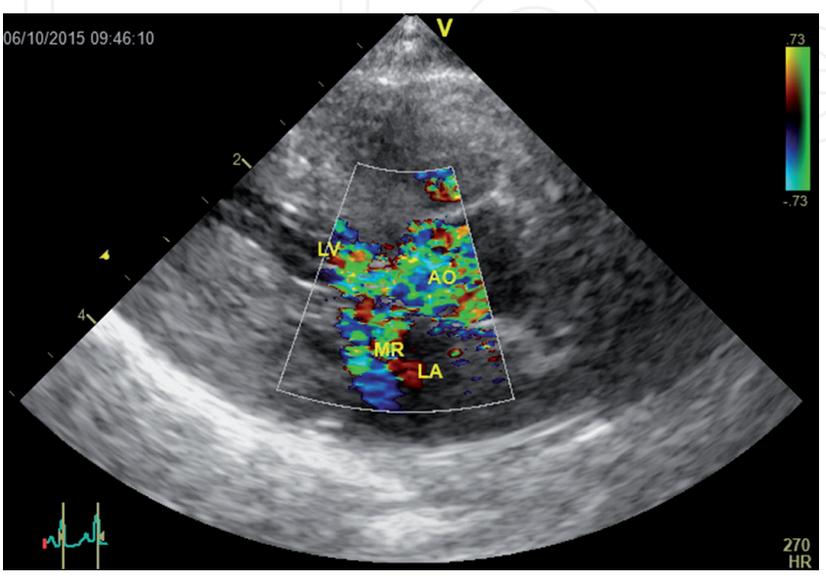


Figure 7.
A color-Doppler flow image of a Sphynx cat with fixed and dynamic subaortic stenosis and concentric hypertrophy of the left ventricle (LV) with concurrent mitral regurgitation (MR).

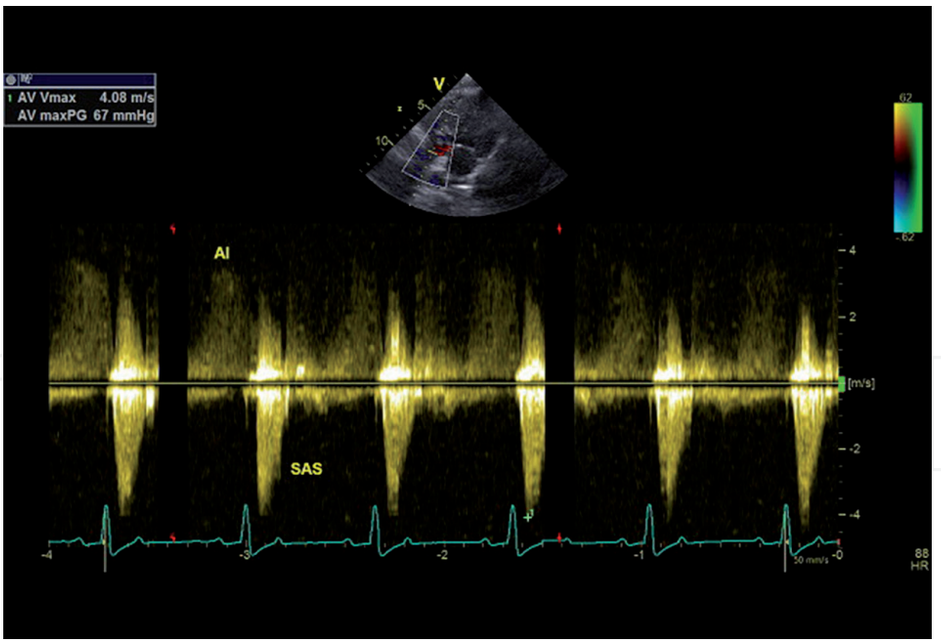


Figure 8.
Continuous wave Doppler across the aortic orifice showing a high velocity jet (AS) of 4 m/s below the baseline, which gives a pressure gradient of 67 mmHg and an aortic insufficiency jet in diastole above the baseline (AI).

[49]. In Boxers without murmurs, higher normal velocities are reported, that is, 2.38 m/s due to smaller LVOT [43, 50].

It is important to use low-frequency transducer for Doppler studies to ensure good penetration of tissues and adequate signal strength to obtain good flow recordings of maximal velocities. Diagnostic problem represents dogs with low intensity murmurs and subtle echocardiographic changes. No association was found between heart rate and aortic velocity [41].

Aortic stenosis has been graded as "mild," with pressure gradients (PG) either from 16 to 40 mmHg (corresponding to aortic velocities, (v), of 2.0–3.16 m/sec) or from 20 to 49 mmHg (corresponding to velocities of 2.25–3.5 m/sec, "moderate," with PG either from 40 to 80 mmHg (v = 3.1.6–4.5 m/sec) or 50 to 80 mmHg (v = 3.5–4.5 m/sec), and "severe" with PG above 80 mmHg, corresponding to velocities over 4.5 m/sec [2, 15]. Pressure gradients derived by Doppler echocardiography showed good agreement with direct pressure measurements, especially for mean gradients [51].

10. Radiography and computed tomography

Thoracic radiographs may appear normal in dogs with AS/SAS; however, in severe cases, LV enlargement may be visible due to LVH and/or post-stenotic dilation of the aortic arch (**Figures 9** and **10**).

In cases where AS is combined with other defects, pertinent radiographic changes may be apparent. Congestive heart failure is rare in SAS, it might be observed in severe cases or with concurrent mitral regurgitation, aortic or mitral endocarditis [2].

Angiographic methods for further evaluation of aortic stenosis morphology are nowadays replaced with contrast computed tomography (CT) scans where needed in terms of interventional or surgical treatment plans. Cardiac CT angiography allows visualization of cardiac chambers and great vessels as well as coronary vessels through cardiac cycles retrospectively. Evaluation of the coronary arteries in the patient is commonly focused on determining if an aberrant vessel is present, which may relate to a pulmonic stenosis, which can be present concurrently with AS/SAS.

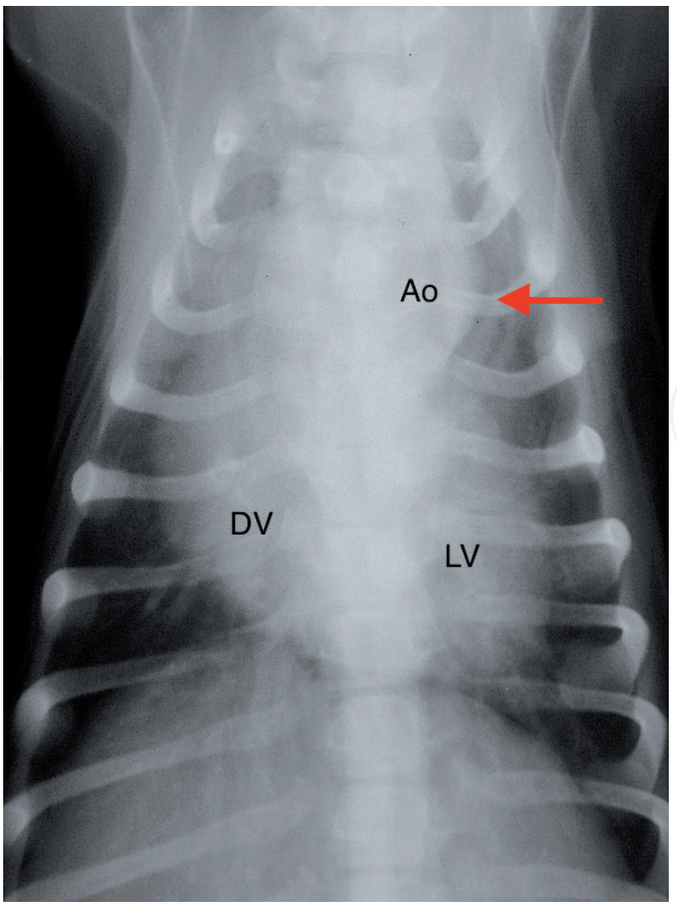


Figure 9.
A dorsoventral thoracic radiograph of a 4-month-old Irish setter with severe aortic stenosis. A post-stenotic dilation of aortic arch is seen (arrow). Ao—aorta, RV—right ventricle, and LV—left ventricle.

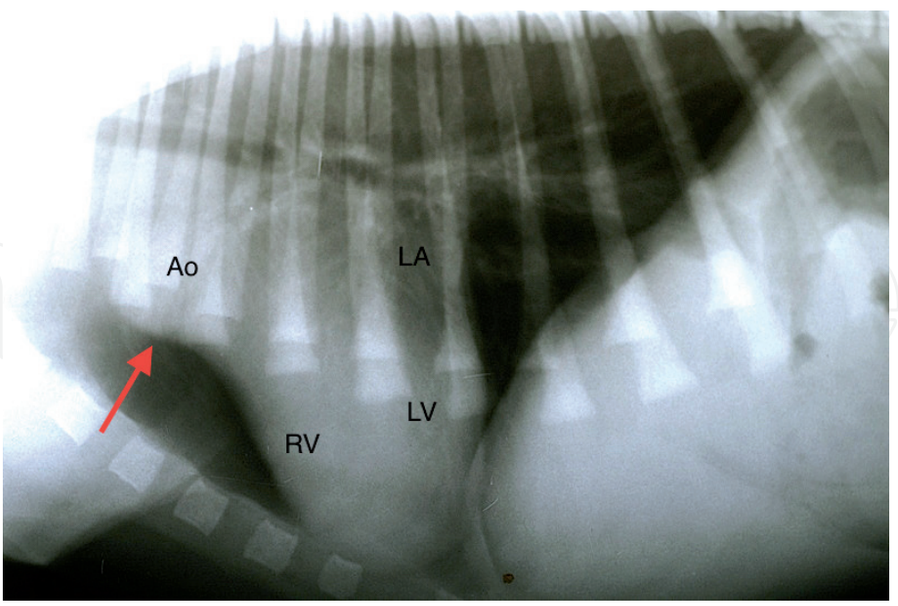


Figure 10.
A right lateral thoracic radiograph of the same dog as in ***Figure 9****, showing a post-stenotic dilation of aortic arch (arrow). DV—right ventricle and LA—left atrium.*

11. Therapeutic possibilities

Prognosis of animals with aortic stenosis depends on the severity of the disease. Mild stenosis usually does not affect longevity; however, the possibility of aortic

endocarditis exists, and antibiotic prophylaxis is recommended for dogs and cats with aortic stenosis [52].

Balloon valvuloplasty, although with an average 50% reduction in PG after ballooning, has not proved to be a long-term solution, because in most dogs restenosis occured [53]; however, in some cases, it may reduce clinical signs [54].

No clear benefit in survival times was seen for dogs that underwent balloon valvuloplasty versus dogs that were treated with atenolol [55].

A new technique with a high-pressure ballooning or a cutting balloon might represent an opportunity for better outcome for dogs with AS/SAS, but to date we have no long-term results [56]. Moreover, aortoseptal angle >160° was associated with better long-term outcomes of treated dogs with cutting and high-pressure balloon [57, 58]. Authors and also others recommend saving patients with moderate and severe AS/SAS against strenuous exercise. Administration of beta-blockers can decrease heart rate, prolong diastole and coronary filling, thereby reducing myocardial hypoxia and protect against arrhythmia. Dogs do clinically well on beta-blockers; however, a study proved no benefit in terms of survival versus untreated dogs with severe SAS [59]. There is no literature on evaluation of other medical treatment.

Surgical options such as closed transventricular valvotomy or open-heart surgery can present an option for dogs with symptomatic or severe AS/SAS; however, also these techniques did not provide long-term benefits or prevent sudden death. Additionally, they are not widely available, and they are risky and costly [60–63]. Hopefully, this might change in the future with the development of minimally invasive techniques and their availability in veterinary medicine.

12. Genetic aspects of aortic stenosis

Comparison of mixed and pure-breed dog populations showed a tendency toward higher incidence of AS in pure-breed dog populations [64]. Among pure-breed dogs, the incidence of AS is increased in herding, working, sporting, mastiff-like, and retriever breeds. The fact that the higher incidence of AS is associated with the increase of inbreeding coefficient in the population supports the suggestion that AS has a genetic component. Online Mendelian Inheritance in Animals (OMIA) database also reports AS in dog as heritable disorder with unclear mode of inheritance [65].

12.1 Evidence for genetic background

Genetic background of AS has been studied in several dog breeds with the aim to decipher its mode of inheritance and causal mutation for it. In the Dogue de Bordeaux, association of AS with several physiological parameters as left-basilar ejection murmur, increased aortic ejection velocity, smaller aortic annulus and decreased aortoseptal angle was discovered and genetic predisposition for AS in Dogue de Bordeaux has been proposed [28]. Familial nature of subvalvular aortic stenosis (SAS) was discovered in Golden retrievers [66] based on pedigree data, where SAS has been observed in several subsequent generations. Although a bit controversial, the most complete data about the genetic base of AS are available for Newfoundland dogs. In the study performed by Reist-Marti [67], an extensive pedigree data set comprising more than 230,000 Newfoundland dogs from European and North American population reaching back to the 19th century has been investigated. Similar to the situation in Golden retrievers, the autosomal inheritance was proposed. In addition, statistically significant association between the inbreeding level and incidence of SAS was also found. However, the most precise information

about the putative molecular background of AS in Newfoundland dogs was discovered by Stern et al. [68]. The authors propose that a three-nucleotide insertion in the genomic region, coding for phosphatidylinositol-binding clathrin assembly protein (PICalM) is associated with the appearance of AS. The pedigree evaluation, similarly as in Newfoundland dogs, supported an autosomal dominant mode of inheritance. The authors demonstrated the presence of PICalM in the canine myocardium and in the area of the subvalvular ridge immunohistochemically, which is supporting the assumption that PICaIM has a role in development of AS.

In Boxers, AS seems to have a genetic background too; however, the causal locus (loci) has not been identified yet. The higher risk for AS in Boxers might be associated with some breed-specific conformational traits, like small aortic annulus and steep aortoseptal angle [69]. The incomplete penetrance of modifier genes together with autosomal dominant mode of inheritance may be the expected genetic base for AS in Boxers [32].

12.2 Genetic diagnostics

Due to the rapid development of genome analysis in all species, several novel approaches are available also in dog genetics. From the genetic point of view, dog breeds represent a very special taxonomic group, characterized by extremely long regions of linkage disequilibrium (LD) compared to other species. This enables a very effective identification of causal genomic regions associated with monogenic genetic disorders using relatively small groups of animals in case versus control format of studies. The most frequently used strategy in this context is genome-wide association studies (GWAS), which can precisely map location of candidate genes in the genome. The candidate gene regions are then further screened for polymorphic sites using the targeted sequencing strategy in order to find causal mutation for genetic disorder (**Figure 11**). However, complex traits, where a larger number of loci are involved in phenotype shaping, represent a much more difficult task and normally require a larger number of individuals for genetic studies.

12.3 Advices for breeding in the future

The number of registered inherited disorders in dogs is permanently growing (over 400 disorders), and in many dog breeds, the point is reached where for the

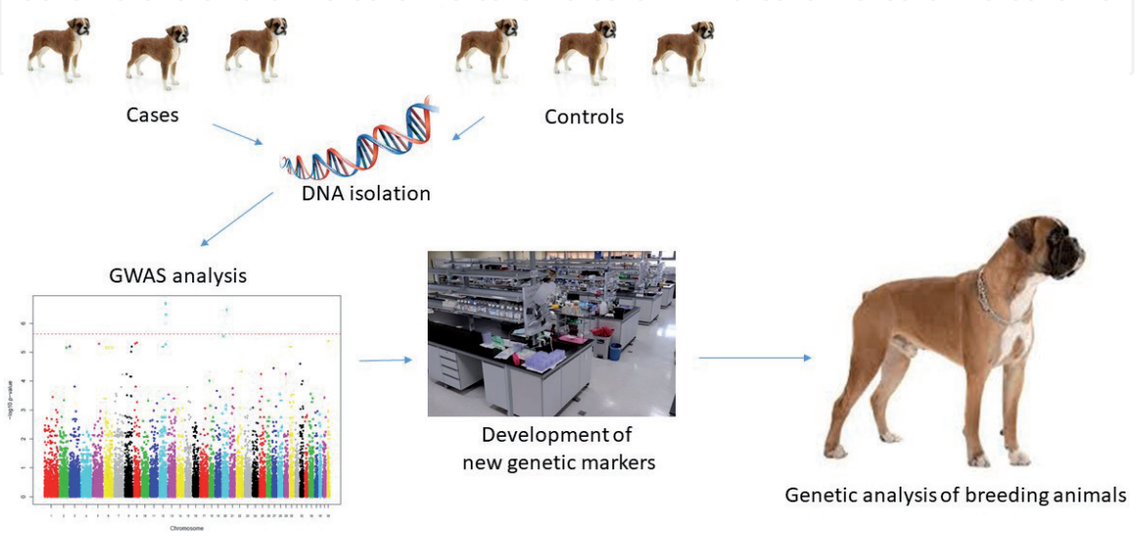


Figure 11.
Summary of development and application of genetic markers for diagnosis of hereditary diseases.

successful breeding against spreading genetic disorders within the breed requires new strategies in combination with currently available breeding schemes. The widespread use of a popular sire caused the overrepresentation of genomes of a low number of sires in many breeds. As a consequence, the effective population size reduced drastically and the risk for rapid dissemination of monogenic disorders within the population increased significantly. The accessibility of reliable genetic tests for detection of carriers of recessive disease-associated alleles represents an important tool for reduction or even elimination of genetic disorders from pure-breed populations. Increasing the number of breeding animals (especially males), controlled introgression of genetic material into closed pure-breed populations, and application of advanced breeding strategies are measures, which will help the breeders to keep genetic pools of different dog breeds healthy.

13. Future perspectives and conclusions

Aortic/subaortic stenosis has a guarded prognosis if moderate to severe; however, efforts have been made in several aspects to fight the disease. First, screening programs have lowered the incidence of the disease (Bussadori 2006, personal unpublished data), and secondly, interventional methods have advanced and might give better prognosis for severely affected dogs; on the other hand, there is still room for surgical methods to take place in veterinary medicine and be more readily available. The genetic background for aortic stenosis is not completely known; however, several mutations, associated with the disease in different breeds, allow development of strategies for genetic screening which would reduce the risk for the disease in pure-breed dogs.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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