

Tricuspid valve dysplasia in dogs

Tricuspidalisdysplasie bij de hond

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A BSTRACT

A general overview of tricuspid valve dysplasia in dogs is presented in this review. This congenital disease has been described in numerous large dog breeds but especially the Labrador retriever is predisposed. The condition is relatively uncommon, with a prevalence of approximately seven percent of all congenital heart diseases in dogs. The asymptomatic phase may last for several years and depends on the severity of the valve malformation. In the clinical phase, exercise intolerance, fatigue, anorexia, cardiac cachexia, dyspnea and signs of right-sided congestive heart failure can be present. Echocardiography including Doppler imaging is warranted to confirm the diagnosis. Curative treatment involves surgical valve replacement but is technically challenging and still in its experimental phase in dogs. As such, treatment in dogs involves the administration of supportive medication once the dogs develop symptoms of congestive heart failure and consists of diuretics, ace-inhibitors and positive inotropic drugs.

SAMENVATTING

In dit artikel wordt een gedetailleerd overzicht gegeven van de verschillende aspecten van tricuspidalisklepdysplasie bij honden. Deze aangeboren aandoening werd beschreven bij diverse grote hondenrassen maar voornamelijk de labrador-retriever is gepredisponeerd. Tricuspidalisklepdysplasie is relatief zeldzaam met een prevalentie van ongeveer zeven procent van alle congenitale hartafwijkingen bij de hond. De asymptomatische fase kan meerdere jaren duren en hangt voornamelijk af van de ernst van de afwijking. Tijdens de klinische fase kunnen inspanningsintolerantie, vermoeidheid, anorexie, cardiale cachexie, dyspneu en tekenen van rechterharthalen aanwezig zijn. Echocardiografie inclusief een dopplersonderzoek is noodzakelijk om de diagnose te bevestigen. Een definitieve behandeling bestaat uit het chirurgisch vervangen van de klep maar dit is technisch moeilijk en bevindt zich bij honden nog in de experimentele fase. Een ondersteunende therapie wordt ingesteld zodra de hond symptomen van congestief hartfalen ontwikkelt en bestaat uit het toedienen van diuretica, ace-inhibitoren en positief-inotrope farmaca.

INTRODUCTION

Tricuspid valve dysplasia (TVD) is a congenital heart malformation that usually manifests itself as tricuspid valve insufficiency and more rarely as tricuspid stenosis (Kittleson, 1998; Barre et al., 2012; Beijerink et al., 2017). When the tricuspid valve leaflets are displaced more apically in the right ventricle (sometimes called “atrialization of the ventricle”), the disease is called Ebstein’s anomaly. In humans, both TVD and Ebstein’s anomaly are uncommon diseases that show poor prognosis with high mortality rates in

utero and shortly after birth, because severe abnormal morphology of the valve results in early death (Barre et al., 2012). In less severe cases, the disease corresponds with an average mortality risk of only 1 to 1.4 percent per year during infancy and adulthood (Malvindi and Viola, 2015). In dogs, the initial prevalence of TVD in utero is unknown. In juvenile and adult dogs, the prognosis is similar to humans and depends primarily on the severity of the malformation. Dogs with small insufficiencies usually have a normal life span (Beijerink et al., 2017). In human medicine, cu-

rative treatment entails artificial valve repair or replacement, while in dogs, only medicinal therapy is currently used as surgical repair is still experimental (Arai et al., 2011; Bristow et al., 2017).

Embryology, anatomy and physiology of atrioventricular valves

In mammals, atrioventricular valve formation occurs in the late phase of the first trimester of gestation. The leaflets of the tricuspid and mitral valve originate from the atrioventricular cushions and a diverticulation of the ventricular wall (McGeady et al., 2006). The valve tissue receives myocardial signals leading to mesenchymal cell death, transformation of endocardial cells and ultimately, to formation of the valve leaflets. Because the valves partially derive from mesenchymal tissue that was originally attached to the myocardium, the valves remain anchored by muscular structures to the ventricular walls. These structures are gradually replaced by dense connective tissue, the chordae tendineae, which ultimately connect the valvular leaflets to the papillary muscles (Kittleson and Kienle, 1998; Fox et al., 1999; Andelfinger et al., 2003; McGeady et al., 2006).

In humans, the tricuspid valve (TV) is composed of three leaflets while in dogs, it has been reported that the TV may consist of two to five leaflets (Alves et al., 2008). The majority of dogs have a TV that is composed of three or four leaflets. In valves containing two or three leaflets, the septal leaflet is larger than the mural (parietal) leaflet and, if present, angular leaflet. The septal leaflet is semicircular in shape and located superior to the interventricular septum. The mural leaflet is more flexible. It starts at the tricuspid annulus and extends slightly more towards the right ventricular apex than the septal leaflet. Consequently, the mural leaflet is more essential than the septal leaflet for an effective closure of the valve during systole (Kittleson and Kienle, 1998; Sisson et al., 1999; Chetboul et al., 2004). In dogs with valves that are composed of four leaflets, the fourth leaflet is located between the septal and the mural leaflet and is called the septoventral leaflet. Exceptionally, a fifth leaflet may be present between the septal and angular leaflet. In these cases, the septal and mural leaflets are less prominent (Alves et al., 2008). The leaflets are anchored by the chordae tendineae to the papillary muscles and papillae. These three structures prevent the leaflets to collapse into the atrium during systole (Kittleson and Kienle, 1998).

During early diastole, ventricular pressures fall rapidly and when the ventricular diastolic pressures become equal to the atrial pressures, the atrioventricular valves open passively, resulting in a rapid blood flow from the atria into the ventricles. At the end of the diastole, the velocity of the blood flow across the valves slows down as the ventricular filling peaks. At this point, the atrioventricular valves partially close. During atrial systole, the valves reopen and provide

the final ventricular filling. The atrioventricular valves close when the ventricular pressure exceeds atrial pressure, resulting in the initiation of the ventricular systole. (Kittleson and Kienle, 1998; Ware, 2013).

Pathophysiology of tricuspid valve dysplasia

Tricuspid valve dysplasia represents an abnormal structure or position of the valve leaflets, the chordae tendineae and/or the papillary muscles and includes elongation, shortening, fusion, and/or thickening of the chordae tendineae, direct insertion of the TV onto the papillary muscles and atrophy, hypertrophy, fusion and/or malpositioning of the papillary muscles (Sisson et al., 1999; Tran-Cong et al., 2004; Boon, 2011; Beijerink et al., 2017).

In human medicine, a grading system based on the type of malformation has been described for TVD (Formigari et al., 1993). These grades negatively correlate with the developmental differentiation of the valve during embryogenesis. Grade I represents myxoid changes of the leaflets and chordae tendineae; grade II represents thickened and often retracted leaflets, and grade III represents extreme dysplasia of the leaflets (Formigari et al., 1993). More recently, a novel grading system that could guide surgical management, has been published (Gupta et al., 2011).

The most common manifestation of TVD in humans and dogs is valve insufficiency. The increased systolic inflow creates right atrial volume overload resulting in an atrial dilation and ventricular accommodation (Ware, 2013; Beijerink et al., 2017). The increased right ventricular end diastolic volume causes eccentric hypertrophy of the right ventricle and allows the right ventricle to eject a larger volume to compensate for the decreased stroke volume caused by the regurgitation over the TV. In this stage, the heart can still compensate the TVD (Sisson et al., 1999).

When the disease progresses, the right heart size keeps on increasing and, as such, the TV annulus widens as well (Kittleson, 1998). It has been proven in other animal species that reactivation of the embryonic pathways for leaflet growth may result in the adaptation of the leaflets, but, obviously, this increase in size does not compensate adequately to prevent further worsening of the regurgitation (Chan et al., 2017). This vicious circle ultimately results in a massive regurgitation with loss of compensatory mechanisms, an increased right atrial pressure and right-sided congestive heart failure, in combination with systemic congestion and a decreased forward flow into the pulmonary vasculature. The left heart becomes underloaded and in the end, a decrease in systemic blood flow occurs. In rare cases, atrial fibrillation and supraventricular tachycardia have been described in dogs with severe TVD (Kittleson and Kienle, 1998; Sisson et al., 1999; Tilly and Smith, 2011; Ware, 2013; Beijerink et al., 2017).

Tricuspid stenosis is another potential manifestation of TVD. Congenital stenosis has been less frequently described in dogs than valve insufficiency,

but both abnormalities may also be present concomitantly in the same valve (Sisson et al., 1999). In humans, true congenital tricuspid stenosis appears to be rare; yet acquired tricuspid stenosis is relatively common in patients with rheumatic heart disease (Brown and Thomas, 1995). The stenotic component may cause a ventricular inflow obstruction with an elevated atrial pressure and an increased peak velocity of the blood flow from the atrium in the ventricle at the level of the TV during diastole. In severe cases of TV stenosis, a limited cardiac output results in a hypoplastic right ventricle with secondary hypotension, syncope and collapse (Sisson et al., 1999; Tran-Cong et al., 2004; Boon, 2011; Ware, 2013; Beijerink et al., 2017). In a case report by Kunze et al. (2002), chronic cyanosis due to high atrial pressure and right-to-left atrial shunting have been described in a dog.

The congenital cardiac abnormality, in which the basal attachments of one or both tricuspid valve leaflets are displaced more apically into the right ventricle with an ineffective closure of the TV as a consequence, is called Ebstein's anomaly (Takemura et al., 2003). In humans, this abnormality is more commonly described than TVD (Malvindi and Viola, 2015). The etiology of Ebstein's anomaly in dogs has not been investigated yet, but in humans, risk factors, such as previous miscarriages, maternal exposure to benzodiazepine and varnish, and the intake of lithium have been identified (Warkany, 1988; Correa-Villasenor et al., 1994; Takemura et al., 2003).

Both in humans and dogs, TVD may occur as a single disease or in combination with other congenital cardiac malformations like mitral valve dysplasia, pulmonic stenosis and atrial and ventricular septal defects (Kittleson, 1998; Sisson et al., 1999; Hoffmann et al., 2000; Famula et al., 2002).

PREVALENCE

Tricuspid valve dysplasia represents approximately two to seven percent of all congenital cardiac malformations in dogs (Tidholm, 1997; Baumgartner and Glaus, 2003; Schroppe, 2015). Important is that a high percentage of neonate and fetuses with severe TVD are likely to die during gestation or shortly after, so the true prevalence is assumed to be higher than reported (Tran-Cong, 2004; Piantadosi, 2011).

BREED AND SEX PREDISPOSITION FOR TRICUSPID VALVE DYSPLASIA AND HEREDITARY ASPECTS

The most affected breed with TVD and Ebstein's anomaly is the Labrador retriever (Kittleson, 1998; Chetboul et al., 2004; Sousa et al., 2006; Tilly and Smith, 2011; Paslawska et al., 2013), followed by the boxer, German shepherd dog, old English sheepdog, Great Dane, Weimaraner, golden retriever, English

bulldog, Dogue de Bordeaux and Irish setter (Liu and Tilley, 1976; Konreich and Moise, 1997; Chetboul et al., 2004; Ohad et al., 2013). Potentially affected small breed dogs include the Yorkshire terrier, beagle, English cocker spaniel, French bulldog and poodle (Paslawska et al., 2013). The majority of the dogs are pure bred dogs (Chetboul et al., 2004).

No clear sex predisposition has been found. In two studies, males seemed to be more affected than females (Tilly and Smith, 2011; Paslawska et al., 2013), whereas in another study (Oliveira et al., 2011) more females were diagnosed with TVD. In a recent prevalence study concerning congenital heart diseases in dogs, one male and one female with TVD were described (Schroppe, 2015).

The increased prevalence of TVD in some dog breeds suggests a genetic predisposition (Beijerink et al., 2017). Tricuspid valve dysplasia has been described in Labrador retrievers as a monogenic autosomal dominant trait with reduced penetrance and with a potential susceptibility locus on chromosome 9 (Andelfinger et al., 2003; Andelfinger et al., 2004). This finding was the first worldwide successful genome mapping of a locus linked to a congenital heart malformation in the dog. In another report, the heritability for TVD in the Labrador retriever has been estimated to be 0.71 but, contrary to the previous study, a recessive inheritance has been suggested (Famula et al., 2002).

In the Dogue de Bordeaux, the mode of inheritance for TVD appears to be autosomal recessive (Ohad et al., 2013). The heritability and mode of inheritance has not yet been established in other dog breeds (Tilly and Smith, 2011).

CLINICAL FEATURES

The severity and the onset of clinical signs depend on the severity of the valve malformation. Many dogs are asymptomatic for several years; fifty percent of dogs diagnosed with TVD in the study of Paslawska et al. (2013) were free of clinical symptoms at the time of diagnosis. In the symptomatic phase, exercise intolerance in combination with a heart murmur on physical examination is the most common symptom (Chetboul et al., 2004). Anorexia and cardiac cachexia are also frequently observed. Additionally, jugular vein distension and pulsation are common findings. Hepatomegaly and ascites may occur in case of right-sided congestive heart failure (Beijerink et al., 2017).

DIAGNOSIS OF TRICUSPID VALVE DYSPLASIA

The tentative diagnosis of TVD can be made based on physical examination, radiography and electrocardiography, but echocardiography is necessary to confirm the diagnosis.

On physical examination, a right-sided holosystolic heart murmur may be heard but it is not necessarily present (Ware, 2013). The intensity of the murmur does not correlate with the severity of the disease; dogs with a relatively soft systolic murmur may have severe malformations. Rarely, a soft diastolic rumble can be auscultated that is suggestive for a concurring tricuspid stenosis. In case of congestive heart failure, a murmur may no longer be present because of the loss of resistance of the valve leaflets against the regurgitation. In this stage of the disease, an increased jugular venous pressure, ascites and pleural effusion may also be present (Kittleson, 1998; Sisson et al., 1999; Chetboul et al., 2004; Beijerink et al., 2017).

Thoracic radiographs of dogs with severe TVD may reveal an impressive right atrial enlargement (Figure 1). Because of the large appearance of the right atrium, the complete right heart may seem enlarged and the apex is often pushed towards the left side of the thorax. The large right atrium can be seen as a well-delimited structure in the thorax. When this abnormality is seen in a young dog with a severe heart murmur located at the level of the TV, this finding is pathognomonic for severe tricuspid regurgitation. In that case, the dog should be referred for echocardiography since TVD is the most likely primary problem (Kittleson, 1998). Tricuspid valve stenosis can be suspected when

the right atrium is severely enlarged without clear radiographic signs of ipsilateral ventricular enlargement (Beijerink et al., 2017).

Additionally, the heart shadow may have a globoid appearance similar to that seen in case of pericardial effusion and dilated cardiomyopathy. Caudal vena cava distension, pleural and peritoneal effusion and hepatomegaly may be appreciated on thoracic radiographs in severe cases of TVD (Kittleson, 1998; Tran-Cong, 2004; Ware, 2013; Beijerink et al., 2017).

On electrocardiogram (ECG), right axis deviation and splintered QRS complexes are the most common findings in dogs with severe TVD (Beijerink et al., 2017) (Figure 3). Other signs of right atrial and right ventricular enlargement may also be present, such as tall P-waves and deep Q- and/or S-waves, respectively. Massive right atrial enlargement may lead to supraventricular tachyarrhythmias including atrial fibrillation. In dogs with Ebstein's anomaly, a tall P-wave in combination with hypervoltage of the T-wave may be noticed (Kittleson and Kienle, 1998; Chetboul et al., 2004; Sousa et al., 2006; Ware, 2013). However, these findings are not specific for right atrial enlargement and an absence of these findings does not exclude right atrial enlargement (Kittleson, 1998). In two case reports described by Sousa et al. (2006), echocardiography revealed severe right atrial

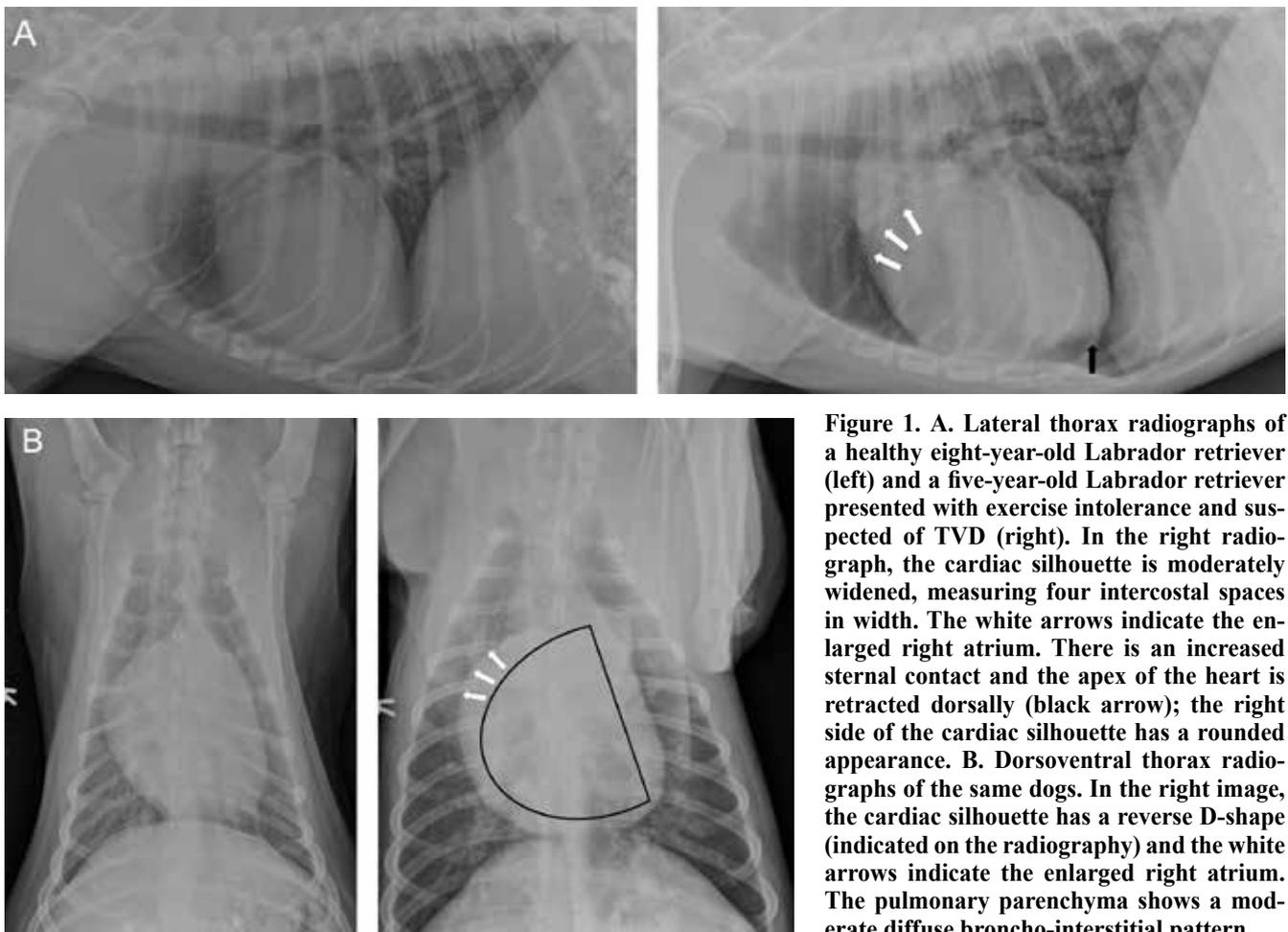


Figure 1. A. Lateral thorax radiographs of a healthy eight-year-old Labrador retriever (left) and a five-year-old Labrador retriever presented with exercise intolerance and suspected of TVD (right). In the right radiograph, the cardiac silhouette is moderately widened, measuring four intercostal spaces in width. The white arrows indicate the enlarged right atrium. There is an increased sternal contact and the apex of the heart is retracted dorsally (black arrow); the right side of the cardiac silhouette has a rounded appearance. B. Dorsoventral thorax radiographs of the same dogs. In the right image, the cardiac silhouette has a reverse D-shape (indicated on the radiography) and the white arrows indicate the enlarged right atrium. The pulmonary parenchyma shows a moderate diffuse broncho-interstitial pattern.

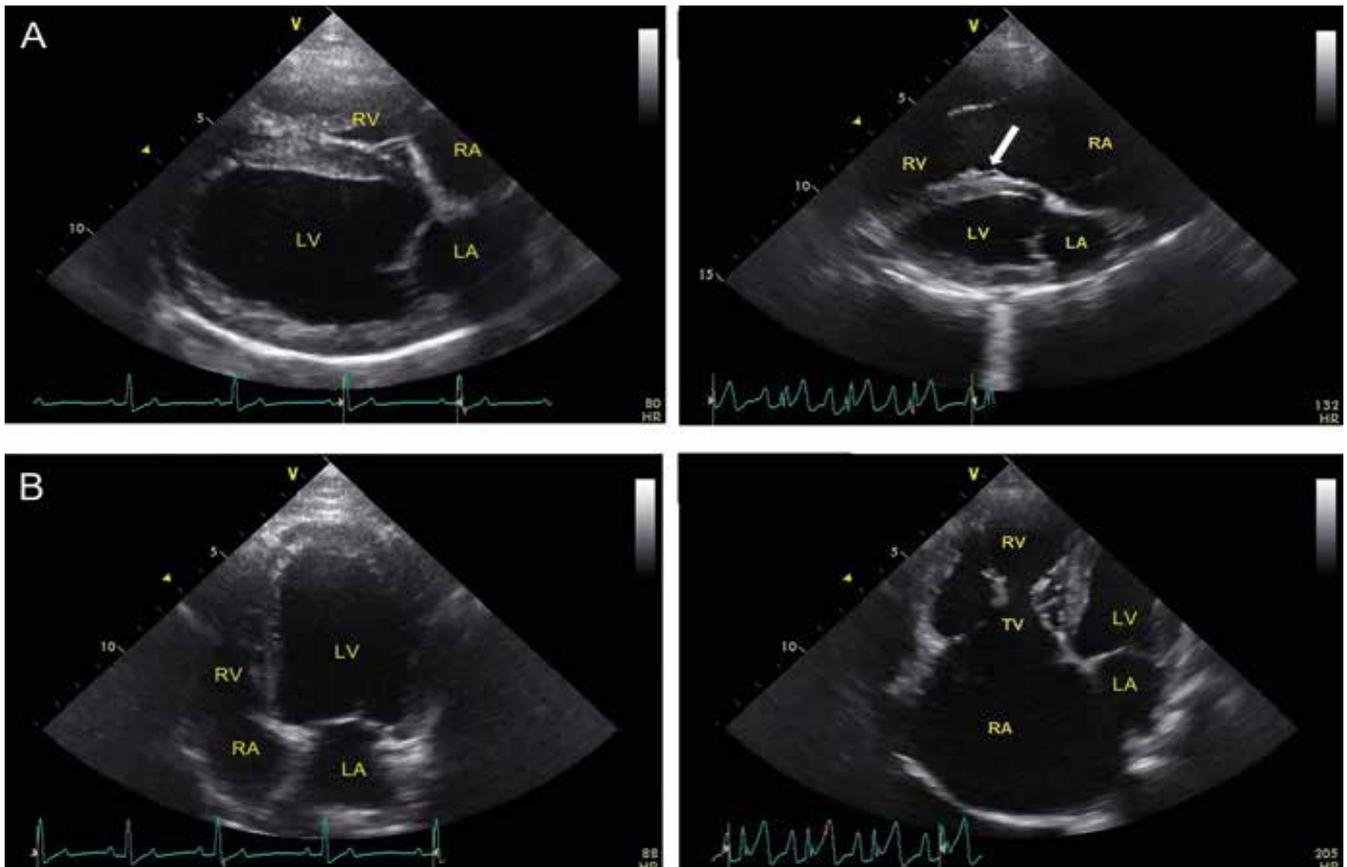


Figure 2 A. Right parasternal four-chamber view of a five-year-old Labrador retriever without echocardiographic abnormalities (left) and a one-year-old Labrador retriever with TVD (right). Note the severe dilation of the right heart and the abnormal morphology of the TV with the septal leaflet tethered to the interventricular septum (arrow). B. Left apical four-chamber view in systole of the same dogs. Note the severe right atrial enlargement and the elongated and thickened anterior leaflet tethered to the interventricular septum.

RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; TV: tricuspid valve.

and ventricular enlargement, although ECG showed only a right axis deviation in both dogs and deep S-waves in one dog.

On echocardiography, the most common findings are the enlarged right atrium and eccentric hypertrophy of the right ventricle (Kittleson, 1998). The right atrial volume overload should be obvious and more severe than the right ventricular volume overload. The left atrium and ventricle are frequently reduced in size. The malformed TV can be visualized on multiple views, but the left parasternal or apical four-chamber view appears to be the view of choice (Boon, 2011). When the septal leaflet is tethered to the interventricular septum, the middle part of the leaflet often moves away from the septum while the ends of the leaflet remain closely opposed to the septum (Figure 2). In these cases, the mural leaflet is typically elongated and closure of the TV is almost effective during systole (Boon, 2011; Beijerink et al., 2017).

Color Doppler imaging is used to identify turbulent regurgitant jets streaming from the ventricle through the incompetent valve into the right atrium during systole. In healthy dogs, trivial tricuspid regurgitation may occur and this finding should not be mistaken for a tricuspid valve disease (Boon, 2011). In dogs with

uncomplicated TVD, the velocity of the regurgitant jet is in the range of 1.5 to 3 m/sec, measured with the continuous wave Doppler. A diastolic pressure gradient can be recorded by Doppler ultrasound across the TV when the TVD results in tricuspid stenosis and is thus complicated (Yuill, 1991; Kittleson and Kienle, 1998; Sisson et al., 1999; Tilly and Smith, 2011; Beijerink et al., 2017). In that case, color flow Doppler studies show increased diastolic flow velocities as high as 2.6 m/s entering the right ventricle while the normal maximal diastolic tricuspid flow velocity is usually less than 1.0 m/s (Brown and Thomas, 1995; Kunze et al., 2002).

In case of Ebstein's anomaly, the right atrium is often severely enlarged and the right ventricle is usually atrialized because of the apical displacement of the tricuspid leaflets (Boon, 2011) (Figure 3). In the normal canine heart, the annulus of the tricuspid and mitral valve are nearly aligned, although the physiologic insertion point of the tricuspid annulus lies slightly more apical than the mitral annulus with a maximum difference of 2 mm. The annulus can be identified on the right parasternal long-axis-four-chamber views of the heart (Boon, 2011).

TREATMENT OF TRICUSPID VALVE DYSPLASIA

Pharmaceuticals provide conservative support and are the most frequently used treatment in dogs (Arai et al., 2011). This treatment is necessary once the dogs show signs of decompensation. The effect of preventive treatment before the onset of clinical signs is unknown (Beijerink et al., 2017). Angiotensin-converting enzyme (ACE) inhibitors are advised in an attempt to prevent the progression of the congestive heart failure by reducing the abnormal cardiovascular remodelling. These inhibitors also reduce sodium and water retention. Positive inotropic products are given to improve right ventricular systolic function and are needed in cases of right-sided cardiac failure. Diuretics such as furosemide are essential to control signs of congestion. As a loop diuretic, furosemide causes excretion of sodium, potassium, chloride, calcium, magnesium and water. A well-balanced diet with low sodium and sufficient energy and protein is also indicated. In case of acute presentation of dyspnea and ascites, oxygen therapy, thoracocentesis and/or abdominocentesis will be necessary (Paslawska et al., 2013; Beijerink et al., 2017). In case of the presence of atrial fibrillation or supraventricular tachycardia, digoxin, calcium channel blockers and beta-blockers can be administered for rate control (Ware, 2013; Beijerink et al., 2017).

The treatment of significant tricuspid regurgitation due to TVD in human medicine exists of surgical valvuloplasty or valve replacement. Both bioprostheses and mechanical prostheses are used for artificial valve replacement. The principal advantage of mechanical prostheses compared to bioprostheses is the durability (Arai et al., 2011; Bristow et al., 2017).

Arai et al. (2011) performed TV replacement in dogs with clinical signs of TV regurgitation due to TVD with bovine pericardial (n=5) or porcine aortic bioprostheses (n=7). Anticoagulation therapy was administered to all dogs to prevent potential thrombosis. In this study, execution and post-operative hospitalization were successful in ten out of twelve dogs. One dog died at home ten days after the surgical intervention due to atrial flutter and cyanosis associated with an uncorrected foramen ovale. Two dogs were euthanized ten and thirteen months after surgery due to implant failure of the bioprosthesis because of inflammatory pannus (Arai et al., 2011). The remaining seven dogs showed complete resolution of TV regurgitation with good quality of life for a median period of 48 months. Other non-fatal complications reported after surgery included thrombosis, atrial flutter or fibrillation and endocarditis.

Bristow et al. (2017) also recently reported the outcome after bioprosthetic valve replacement in nine dogs with clinical signs of congestive heart failure due to TVD. Again, bovine pericardial valves (n=8) as well as porcine aortic valves (n=1) were implanted.

All dogs received anticoagulation therapy to prevent thrombosis. Five dogs had fatal complications in the postoperative period (problems regarding coagulation and septicemia). The median survival time of the four remaining dogs was approximately one year. Of these four dogs, two dogs ultimately died as a result of valve stenosis due to inflammatory pannus or organized thrombus. Thus, outcomes after surgical valve replacement were in this study associated with a high incidence of complications. An explanation for the higher mortality rate in this study than in the study of Arai et al. is difficult as the executed technique was similar in both studies. The only difference was the protocol for the anticoagulation therapy; warfarin therapy was initiated the day after heparin administration, whereas in the study of Arai et al., an interval of two days was respected.

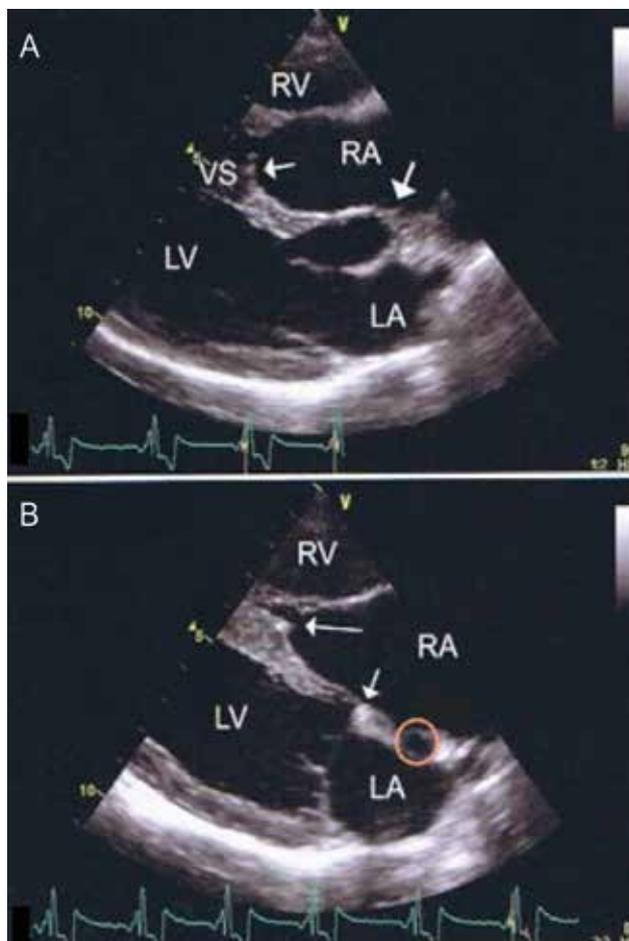


Figure 3. Right parasternal four-chamber views of a dog with Ebstein's anomaly. The tricuspid annulus is displaced apically into the right ventricle. A. The small arrow indicates the displaced TV; the normal point of attachment of the tricuspid valve is shown with the large arrow. B. The long arrow indicates the tricuspid annulus, clearly apically located. The orange circle indicates a concomitant patent foramen ovale. RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; VS: ventricular septum (Adapted from Boon, 2011).

Aside from the complication risks, the specialized technical approach, the necessity of an extra-corporal fluid circulation and the high costs limit the application in veterinary medicine (Sisson et al., 1999; Arai et al., 2011; Paslawska et al., 2013).

The main limitation for the use of bioprosthesis in human medicine is the shorter durability compared to mechanical prosthesis. The degradation of a bioprosthesis begins already after ten to fifteen years, but taking the shorter life expectancy of dogs into account, this might be less important or less of an issue in dogs (Rizzoli et al., 2003; David et al., 2010).

In human medicine, tricuspid stenosis can be surgically corrected by performing balloon valvuloplasty. In three case-reports, transcatheter balloon valvuloplasty in dogs with tricuspid stenosis has been described (Brown and Thomas, 1995; Kunze et al., 2002; Lake-Bakaar et al., 2017) with markedly lower and clinically acceptable diastolic peak velocities at the level of TV several months after surgery. However, recurrence of heart failure may occur.

PROGNOSIS OF TRICUSPID VALVE DYSPLASIA

The prognosis of TVD depends on several factors including the degree of valvular malformation, the presence of other congenital cardiac malformations and the severity of the cardiomegaly. Dogs with small insufficiencies usually have a normal life span (Beijerink et al., 2017). Negative prognostic factors are a high-velocity regurgitant flow through the dysplastic TV during systole, right sided cardiac failure and atrial fibrillation. Some dogs may have a good quality of life for several years under medication while others have a rapid progression of the disease (Beijerink et al., 2017).

The prognosis for Ebstein's anomaly is worse as congestive cardiac failure develops frequently before the age of one year and cardiac arrhythmias are common (Chetboul et al., 2004).

CONCLUSION

Tricuspid valve dysplasia is generally considered to be a relatively rare congenital heart malformation in the dog. The disease can remain asymptomatic for several years. Based on physical examination, radiography and/or electrocardiography, TVD can be presumed, but formal diagnosis is based on echocardiography. Surgical intervention as a curative treatment is still in its experimental phase. The current therapy exists of the administration of positive inotropic drugs, diuretics and ACE inhibitors once the patient shows clinical symptoms.

This condition probably has a genetic base, especially in the Labrador retriever, but also in other

breeds. Further genetic research is necessary to identify the disease-causing mutations for TVD. Because the mutation has not been identified yet, dogs that are related to an affected animal should be screened using echocardiography before breeding.

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