Atrioventricular septal defect in the cat. Description of a case and the embryological features

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Atrioventricular septal defect (AVSD) is a complex congenital heart disease characterized by abnormal development of the atrioventricular junction, leading to a single atrioventricular orifice with a common atrioventricular valve. AVSD can be classified into complete, partial and intermediate forms. The defect is uncommon in cats and there is a paucity of literature on AVSD in this species. In the first section of the article the clinical, instrumental and pathological findings of a partial form of AVSD in a domestic shorthair cat are presented. In the second section the embryological pathogenesis of the condition is discussed in the light of the most recent knowledge about AVSD.

Key words - Congenital heart disease, endocardial cushions, atrioventricular junction, vestibular spine, atrioventricular canal, atrioventricular valves.

INTRODUCTION

Atrioventricular septal defect (AVSD) is a complex congenital heart disease, which includes a spectrum of anatomical defects associated with abnormal development of the atrioventricular (AV) junction or *crus cordis*. This area includes the AV septum and the two AV valves[1]. From a hemodynamic point of view, it is a condition in which there is a left-to-right shunt of blood. According to the current classification of the International Pediatric and Congenital Cardiac Code (IPCCC)[2], the term "atrioventricular septal defect" is to be preferred over "atrioventricular canal defect" and "endocardial cushion defect". The last term is reductive, as it has been clearly demonstrated that the defect does not originate only from an abnormal development of the endocardial cushions[3,4]. AVSD is characterized by the presence of a single AV orifice protected by a common AV valve consisting of five leaflets. Of the leaflets that constitute the AV valve, two are confined to the right ventricle (antero-superior and right mural), one to the left ventricle (left mural), while two are in common to the two ventricles ("bridging" leaflets, which are anterior or superior and posterior or inferior)[5].

The IPCCC distinguishes three subtypes of AVSD: complete, partial and an intermediate form. The complete form is characterized by the combination of a single AV valve, an *"ostium primum"*-type atrial septal defect (ASD-OS1) and a non-restrictive defect in the inlet portion of the ventricular septum (inlet ventricular septal defect, VSD). In this condition a communication is created between the right and left sides of the heart at both the atrial and ventricular levels. In the partial form the five-leaflet configuration of the malformed AV valve apparatus is maintained[6], but there is a bridge of valvular tissue between the anterior and

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posterior leaflets, which divides the common valve into two separate orifices. This bridge is generally anchored to the ventricular septum, reducing the defect to an ASD-OS1 interatrial type of communication (partial AVSD ASD type 1)[3,5]. Less frequently, the valve leaflets fuse with the atrial septum, obliterating the interatrial defect, generating an interventricular shunt in the non-restrictive portion of the inlet (partial AVSD inlet VSD)[3,5]. The intermediate form (intermediate or transitional AVSD) is essentially a partial subtype in which an ASD-OS1 defect and a restrictive defect of the ventricular septum are associated with two separate AV orifices[3]. Another less common form is the Gerbode-type defect, a particular type of anomaly of the membranous interventricular septum, with shunting between the left ventricle and right atrium[3]. This classification has been taken up by veterinary medicine[11,20]. There is a paucity of published literature on this topic in the feline species[8-13]. The most recent publication[11] concerns a collection of 26 patients, including 17 cases of isolated AVSD and 9 cases associated with other congenital heart disorders. The partial form was found to be more frequent (13/17), with the distribution of the ASD type 1 and inlet VSD forms being similar (7/13 versus 6/13, respectively). ASVD has been estimated to account for 5-10% of all congenital heart disorders in cats[14]; there does not seem to be a particular breed-related predisposition (with the exception of a supposed family predisposition in Persian cats[12]) and the distribution between the sexes is similar.

The purpose of this article is to describe a case of AVSD in a cat and discuss the data in the literature, focusing particularly on the anatomical and embryological aspects.

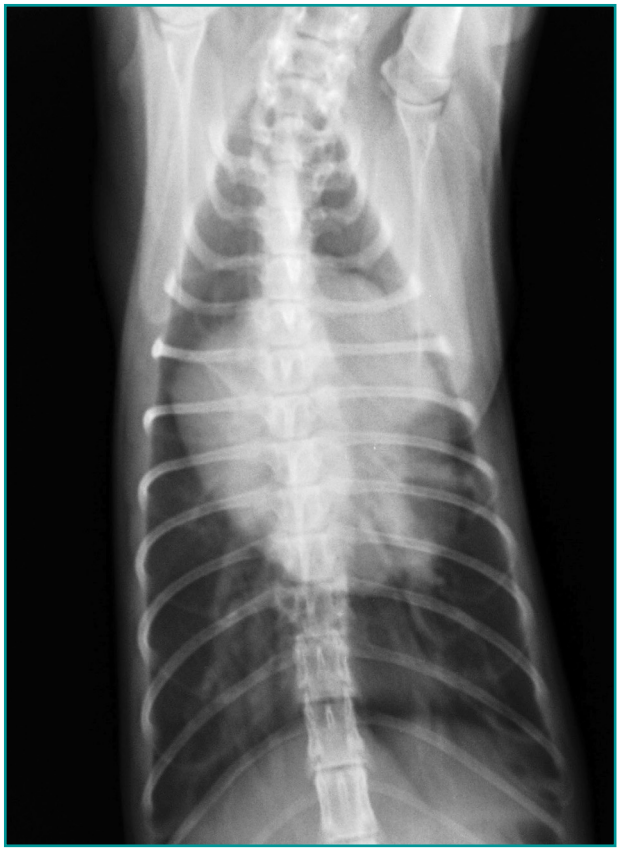

Figure 1 - Chest x-ray, dorso-ventral view. Note the enlargement of the cardiac shadow with a marked left shift of the cardiac apex and an increase in the profile of both atria. Both pulmonary arteries and both pulmonary veins are dilated.

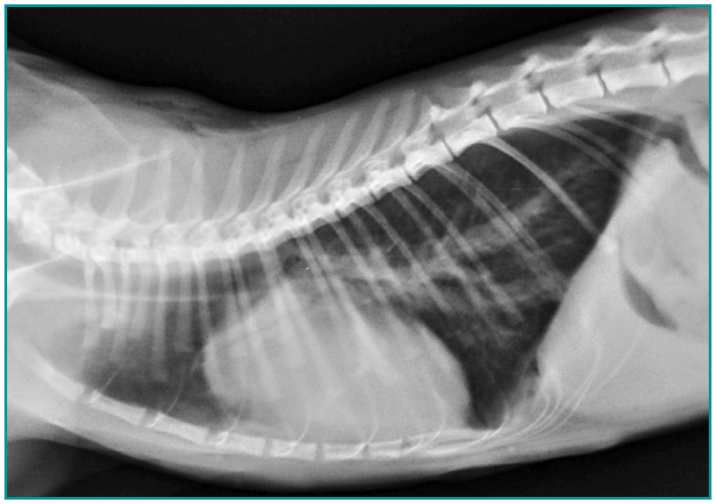

Figure 2 - Chest x-ray, right lateral-lateral projection. The radiograph shows the increased heart-sternum contact, tracheal uplift, distension of the cranial lobar vessels and widespread, increased vascularity in the caudal fields.

Atrioventricular septal defects comprise a spectrum of cardiac defects with abnormal development of the atrioventricular junction.

CASE REPORT

History

The patient was a 5-month old, domestic shorthair, sexually intact female cat weighing 2 kg, which showed an evident growth delay compared to her littermates and had a heart murmur found on auscultation.

Clinical picture

On clinical examination the animal showed a normal sensorium, good hydration, nutrition (5/9)[15] and muscle tone (3)[16]. The oral mucosae were pink with a capillary filling time of less than 2 seconds; the femoral pulses were present bilaterally, were of the same pressure and were synchronous. Respiration was concordant, but tachypneic (40 breaths/min). An obvious precordial thrill was noticeable on palpation of the left precordium. On cardiac auscultation there was a left basal systolic murmur, which irradiated to the right

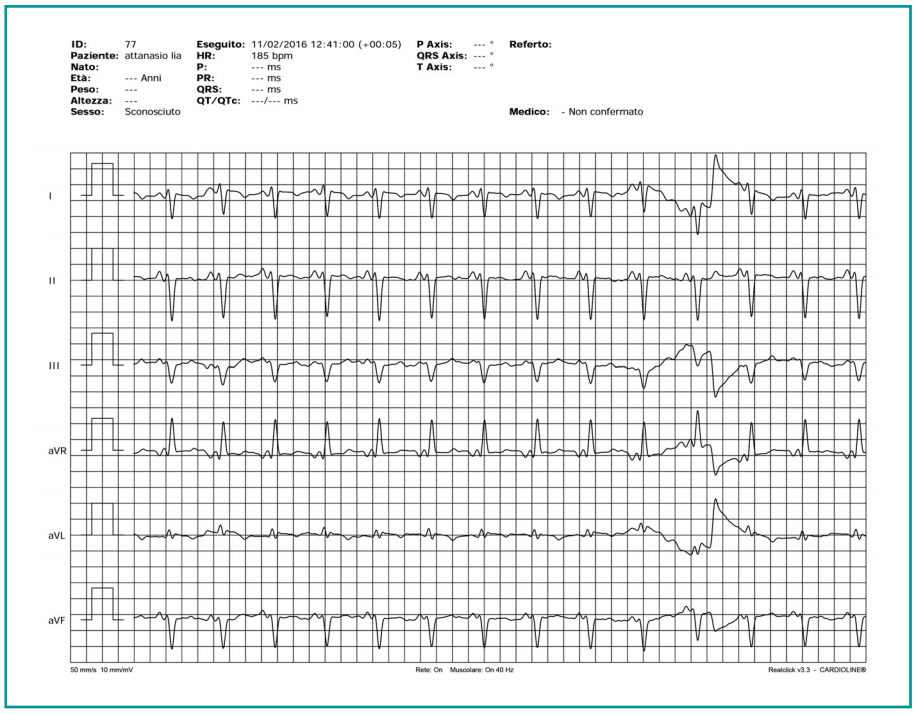

Figure 3
Standard 6-lead ECG examination, performed in right lateral decubitus. Sinus rhythm, P waves of 40 ms, P-Q interval of 22 ms and QRS complex of 58 ms. There is marked right axial deviation (average heart axis -105° on the frontal plane), with *rS* morphology of the QRS complex in both lower limb leads and in DI.

The radiographic examination showed cardiomegaly, together with increased pulmonary flow, while electrocardiography revealed a conduction disorder with an incomplete right bundle branch block.

precordium. The animal's systolic blood pressure (determined by Doppler) was 140 mmHg.
A chest X-ray, performed without sedation[17], showed an enlarged cardiac shadow (cardio-thoracic index of 0.9 [normal, 0.65 ± 0.06][18] and vertebral heart size of 10 [normal cut-off, 8.2][19]) and increased pulmonary blood flow (Figs. 1 and 2). A standard electrocardiogram (Fig. 3) showed an average heart rate of 185 bpm with sinus rhythm and a conduction disorder compatible with complete right bundle branch block[20].
Ultrasound examination of the abdomen determined that the organs and large vessels were in their normal positions.
Segmental echocardiographic examination[21,22] in B-mode showed normal veno-atrial and ventricular-arterial connections and concordant atrio-ventricular connections. The right chambers appeared to be dilated[23].
A large defect measuring 9.3 mm was present in the lower part of the atrial septum (ASD-OS1 type defect) in a parasternal right 4-chamber scan (Fig. 4) (video 0_1). The two AV valves appeared to be separate, but aligned on the same axis on the muscular interventricular septum. The mitral valve was malformed with a short, thickened and irregular septal leaflet and a more developed parietal leaflet. The tricuspid valve had a wide annulus with an elongated anterior leaflet.
The right parasternal short axis scan showed a fissure ("cleft") of the anterior mitral leaflet. The septal end of the leaflet was supported by a papillary muscle in-

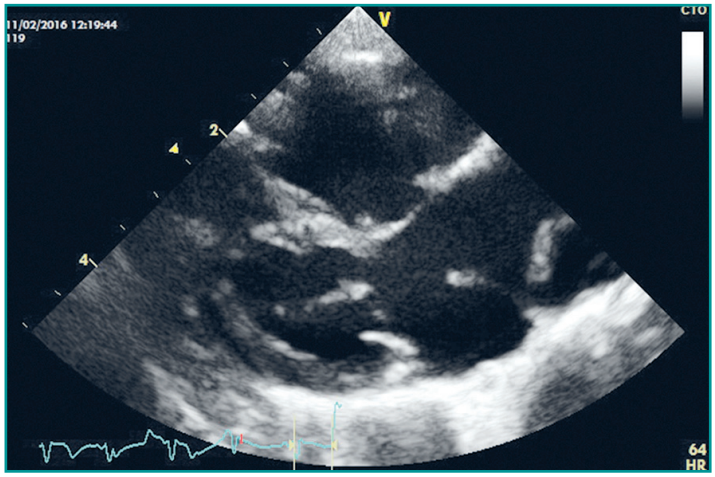

Figure 4 - Echocardiographic examination. Right parasternal long axis scan. Dilatation of the right chambers, a well-aligned interatrial septum, but with a large defect (ASD-OS1 type) are appreciable. The atrioventricular valves are aligned.

Video 0_1
Right parasternal long axis scan. Dilation of the right chambers, the ASD-OS1 defect and the well-aligned AV valves can be seen.
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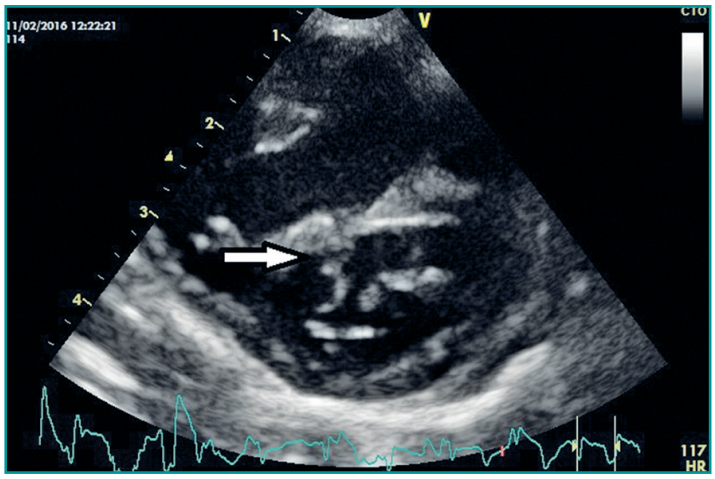

Figure 5 - Echocardiographic examination. Right parasternal short axis scan. "Clover-leaf" appearance of the mitral valve due to the so-called mitral cleft in the anterior leaflet of the mitral valve. Note the insertion of the subatrial papillary muscle (arrow) on the septum.

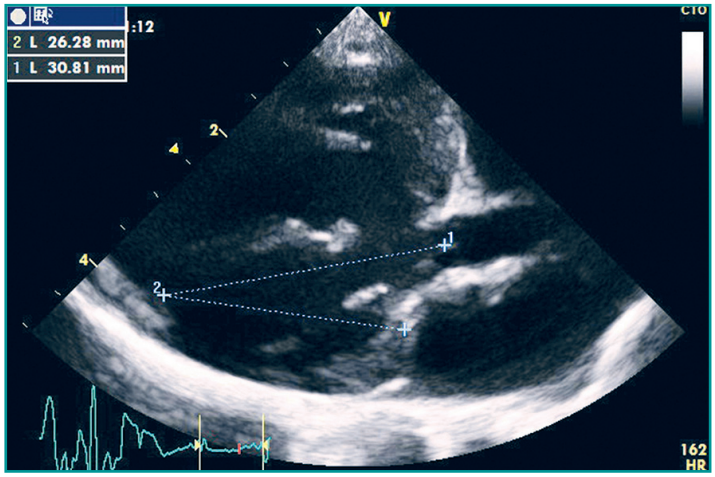

Figure 6 - Echocardiographic examination. Five-chamber right parasternal long axis scan. The elongated appearance of the left ventricular outflow tract is evident.

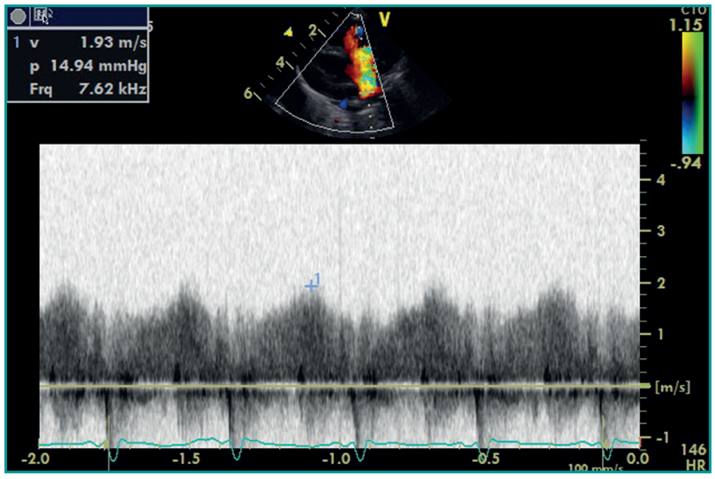

Figure 7 - Echocardiographic examination. Continuous Doppler through the atrial septal defect.

Video 0_2
Right parasternal short axis scan. Dilatation of the right ventricle, the "clover-leaf" appearance of the mitral valve and the insertion of the subatrial papillary muscle on the septum can be noted.
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serted into the septum and its orientation was, therefore, rotated in a cranial sense with respect to the normal insertion of the subatrial papillary muscle (Fig. 5) (video 0_2).

Five-chamber right parasternal long axis scans showed an evident difference between the distance from the apex of the left ventricle on the aortic valve plane and the mitral valve plane, such that the left ventricular outflow tract (LVOT) was elongated, with the deformity having a "goose neck" appearance (Fig. 6)[30-32]. The left ventricle showed normal systolic pump function (ejection fraction: 61%, area/length method, right parasternal 4-chamber view). Colour Doppler studies showed an anterior-directed mitral jet, which, through the atrial septum defect, reached the vault of the right atrium. Furthermore, there was turbulent flow within the atrial septal defect, with a maximum instantaneous velocity of 1.9 m/s (continuous Doppler), equivalent to a maximum instantaneous gradient of 14.9 mmHg and a predominantly left-to-right shunt and early diastolic peak (Fig. 7). Pulsed Doppler showed normal aortic, pulmonary, and mitral flows. The echocardiographic diagnosis was an isolated form of partial AVSD (partial AVSD ASD type 1)[3,26] with a left-to-right shunt and diastolic overload in all four heart chambers, but particularly those on the right.

The echocardiographic examination showed the presence of an interatrial ASD-OS1 type defect associated with a malformed atrioventricular valve and a deformed left ventricular outflow tract.

Treatment based on furosemide (2 mg/kg BID) and ramipril (0.25 mg/kg BID) was initiated. Over the next 6 months the animal's clinical condition improved significantly, according to telephone checks. At 9 months, due to the forced suspension of therapy for about 1 week, the patient developed severe non-responsive pulmonary oedema and was euthanized. The heart was excised and sent for histopathological examination. The lungs could not be removed.

On external examination of the heart, there was marked dilatation of both atria and both auricles together with a pronounced increase in the volume of the right ventricle (double apex heart). On opening the

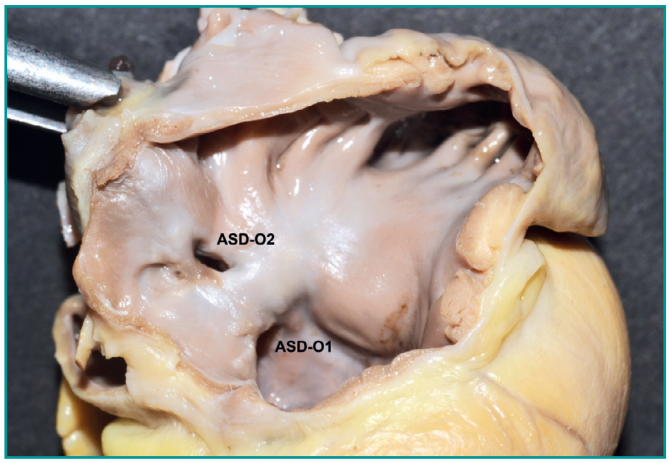

Figure 8 - Opening of the right atrium. Two defects of the interatrial septum can be identified, one of an *ostium primum* type (0.9 cm) and the other an *ostium secundum* type (0.5-0.7 cm). ASD-OS1: *ostium primum* type atrial septal defect. ASD-OS2: *ostium secundum* type atrial septal defect.

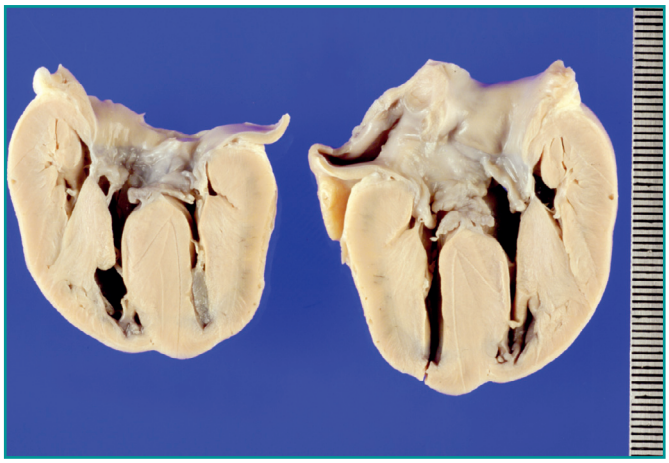

Figure 10 - Midline longitudinal section of the heart. Two orifices communicating with the respective ventricles can be seen.

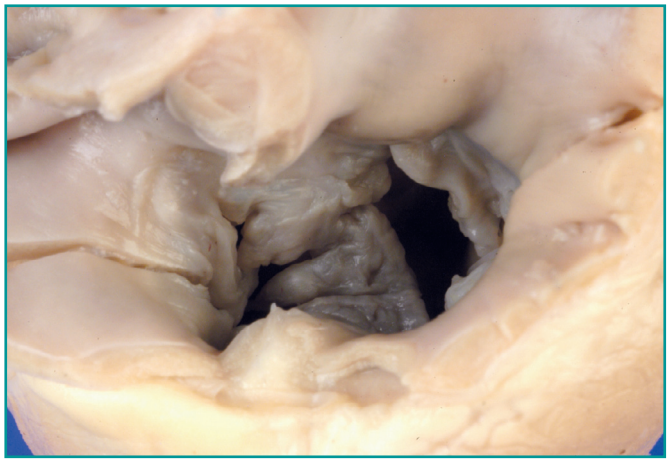

Figure 9 - Atrial floor (after removal of the atria and atrial septum). A single, complex valve annulus can be seen.

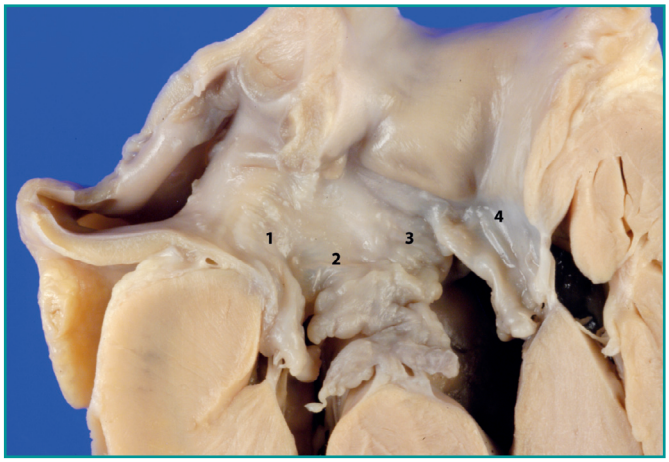

Figure 11 - Detail of the valve structures. A left valvular structure (corresponding to the mitral valve) and a right valvular structure (corresponding to the tricuspid valve) can be noted: each has a parietal leaflet and a bipartite septal leaflet (bridging leaflets). 1: parietal leaflet of the left valve; 2: septal leaflet of the left valve; 3: septal leaflet of the right valve; 4: parietal leaflet of the right valve.

right atrium, two atrial septal defects were seen, one *ostium primum* defect (about 0.9 cm) and the other an *ostium secundum* defect (about 0.5-0.7 cm) (Fig. 8). Following asportation of the atria and of the remaining atrial septum, a single, complex valve annulus could be seen in the atrial floor (Fig. 9), characterized by two orifices that communicated, on the midline longitudinal section of the heart, with the respective ventricles (Fig. 10). This valve apparatus had a left component (corresponding to the mitral valve) and a right component (corresponding to the tricuspid valve).

On midline longitudinal section of the heart, the former comprised a septal component and a parietal component. The latter had a markedly deformed, thickened leaflet and the *chordae tendineae* were severely hypoplastic or absent. In contrast, the septal component appeared to be displaced ventrally with respect to its parietal counterpart and was inserted irregularly at the level of the interventricular septum. It, too, was composed of two markedly deformed, thickened portions located on different planes and poorly developed *chordae tendineae*. The other valvular structure was also composed of parietal and septal components. The parietal component was elongated, irregular, and thickened and its *chordae tendineae* were, in part, more developed than those of its left counterpart. Finally, the septal component was also irregular, thickened and with characteristics similar to those of its left counterpart (Fig. 11). The median longitudinal section of the heart also showed substantial concentric hypertrophy of both ventricles [the proximal portion of the free wall of the left ventricle (i.e., not in correspondence with the papillary muscle) measured 0.9 cm; the

average portion of the left interventricular septum measured 0.9 cm; and the intermediate portion of the right ventricular free wall measured 0.8 cm].
Although the wall thicknesses determined during the post-mortem examination did not
correspond to those measured by echocardiography, the heart undoubtedly had marked concentric hypertrophy of both ventricles and it could be excluded that the increases were artefactual findings. The anatomo-pathological examination excluded primary forms and obstruction of outflow tracts. It must be pointed out that it was not possible to examine the lung parenchyma histologically in order to verify any vascular disorders and that the anatomo-pathological study of the residual portion of the aorta did not show lesions responsible for obstruction.

This article describes the case of a partial AVSD in a cat. The salient echocardiographic features are the ASD-OS1 defect, a mitral "cleft" and the conformation of the left ventricular outflow tract.

DISCUSSION

Here we describe a partial AVSD ASD type 1[3,26] in a cat. The essential anatomical features for a correct echocardiographic diagnosis of this defect consist of a common AV junction with two separate valves, the presence of a mitral "cleft", an interatrial defect such as an ASD-OS1 and different dimensions of the left inflow and outflow tracts, with anterior displacement of the aorta.
Two separate valves can be appreciated at the AV junction, although they lie on a single plane (defined as a "linear" insertion[24]), because of the more apical position of the mitral valve with loss of the normal cardiac "offset"[25]. We have already mentioned in the introduction that the configuration of five leaflets is maintained in the partial form of AVSD[6], but there is a bridge of valvular tissue between the anterior and posterior leaflets, which divides the common valve into two separate orifices. In reality, the terms mitral and tricuspid should be replaced by "left" and "right" valves, respectively.
This bridge is usually anchored to the crest of the interventricular septum, reducing the defect to an ASD-OS1 type interatrial communication (partial AVSD ASD type 1)[3,26]. On echocardiography, the anterior leaflet of the left valve shows a fissure (the "mitral cleft"), with associated mitral regurgitation. In reality, this is not a fissure of the leaflet, but a space between the superior and inferior bridging flaps at the point that they are inserted into the crest of the interventricular septum[27]. The clockwise rotation of the normal insertion of the subauricular papillary muscle into the septum, in a more anterior position, is a further element distinguishing a true "cleft" in a normally conformed mitral valve and a false "cleft" in AVSD[27,35]. The presence of a regurgitant jet is also an important feature for making the differential diagnostic between a partial form of AVSD and an isolated atrial defect. Another important point in the echocardiographic and anatomo-pathological characterization of the defect is that the abnormal development of the AV valves, preventing the normal wedging of the aortic valve between the mitral and tricuspid valves, lead to anterior displacement of the outflow part of the left ventricle, comprising the LVOT, the aortic valve and the aortic root. The result is that the "inlet" is shorter than the "outlet" (in a normal heart they should be of a similar size)[26,53]. Furthermore, this anterior displacement contributes to the LVOT assuming an elongated and narrow form, such as to make the deformity look like a "goose neck" or "swan neck"[28-32]. This appearance, first described in the course of angiographic examinations[33], is also recognizable during an echocardiographic examination in 5-chamber scans (right parasternal and retroxiphoid)[31]. In some situations, this condition creates the anatomical substrate for subaortic stenosis[29-32]. In the case we describe, a normal aortic flow rate and the absence of colour-Doppler turbulence excluded a stenotic phenomenon.
As far as concerns hemodynamic features, in our case the left-to-right shunt occurred between the atria. In a study by Shrope[11], shunting between the atria and between the ventricles was equally prevalent in the partial forms of AVSD, in contrast to the findings in humans, in whom interventricular shunts are less frequent in partial forms of AVSD[3].

The rearrangement of the atrioventricular area causes an alteration of the normal anatomy and electrophysiology of the conduction system.

The rearrangement of the AV area also leads to an alteration of the normal anatomy and electrophysiology of the conduction system. Following this rearrangement, the position of the AV node is more posterior and inferior within the Koch triangle and, consequently, a longer bundle of His is required to reach the ventricles[3]. The most common resulting disturbance of the conduction of the electrical impulse in the heart is right bundle branch block[3,39,48,49]. This was found in our case and also in the study by Schrope[11]. In addition, delayed intra-nodal conduction can occur as a result of

the perturbations that the persistence of the *ostium primum* induces in the development of the conduction system in the so-called "AV junction area"[39].

The key embryo-pathogenic feature of AVSD is, in brief, abnormal development of the AV septum and AV valve complex. It has been shown, from experimental work on chicken, rodent and human embryos[39-41], that during the stages of cardiac development, the AV canal not only represents the point of passage between the primitive atrium and the ventricle, but also plays a crucial role in the correct separation between the right and left hearts, through the formation of the two AV valves, the AV septum (which joins the interatrial septum with the interventricular septum) and, above all, of the annular fibrous complex used to isolate the atria electrically from the ventricles. In this process of septal formation within the AV canal, the so-called **"AV mesenchymal complex"** (AVMC) plays a fundamental role. This complex consists of the group of endocardial cushions (EC, which can be distinguished into a superior, an inferior and two lateral cushions), and the *septum primum* with its most ventral part called the **"mesenchymal cap" (MC)** and the dorsal mesenchymal protrusion **(DMP)**[42-44] (Fig. 12a).

The EC develop at the time of the start of the looping process and consist of aggregates of endocardial cells, which, appropriately stimulated by lipophilic growth factors (essentially chondroitin sulphate and glycosaminoglycans) secreted by myocardial cells[45], transform into mesenchymal cells, which proliferate and occupy the space inside the AV canal. The superior EC, in contact with the internal curvature, and the inferior CE, in contact with the external curvature, will contribute to form the septal leaflets of the mitral and tricuspid valves, as well as the AVMC[46]. The MC[50,51] is formed of an aggregate of mesenchymal cells, of endothelial derivation, which occupy the ventral apex forming the *septum primum*. As it develops, it merges with both the dorsal EC and the DMP, obliterating the *ostium primum*[52]. The **DMP** is a mesenchymal structure derived from the "second cardiac field" of the venous

The atrioventricular mesenchymal complex comprises all four endocardial cushions, the mesenchymal cap and the dorsal mesenchymal protrusion.

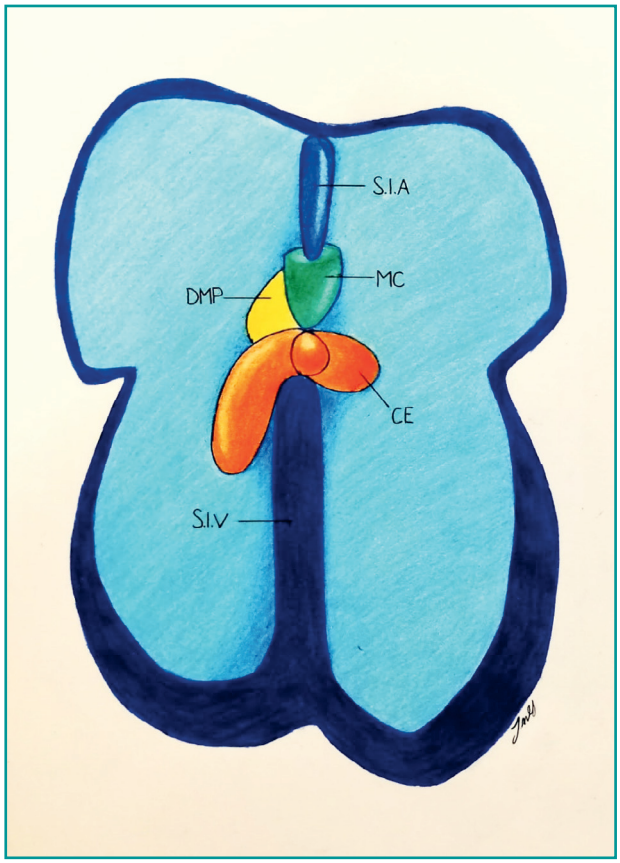

Figure 12a - Diagram of the physiological development of the atrioventricular septum. The interatrial septum (IAS), interventricular septum (IVS), mesenchymal cap (MC), dorsal mesenchymal protrusion (DMP) and endocardial cushions (EC) are indicated.

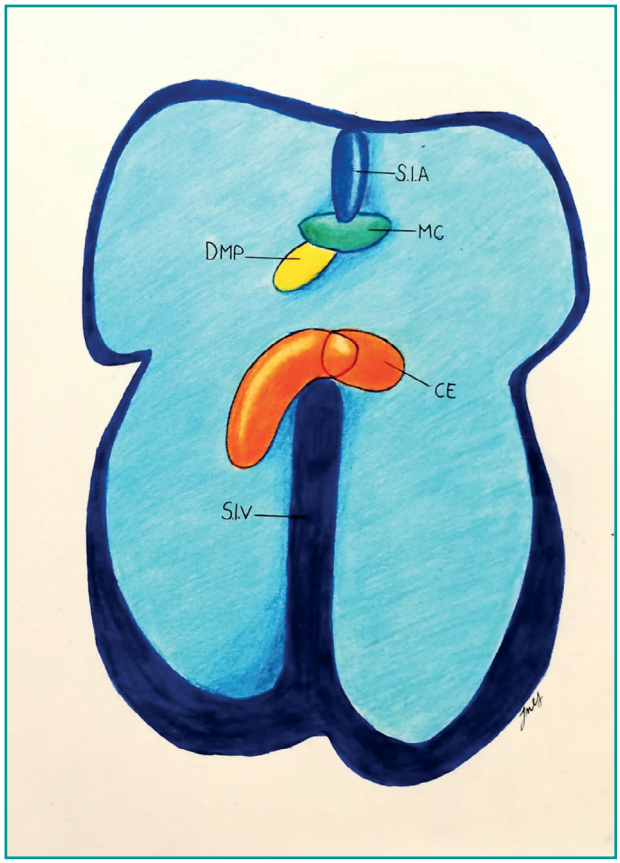

Figure 12b - Schematic representation of the theory on the genesis of partial atrioventricular septal defect (AVSD), with defective development of the mesenchymal cap (MC) and dorsal mesenchymal protrusion (DMP).

pole, located at the base of the interatrial septum[42]. Originally defined by His as the "vestibular spine"[44,47], the DMP develops, during the terminal phases of looping, in correspondence with the floor of the common atrium, topographically close to the pulmonary veins[4]. The role played by the DMP is to merge with the MC to occupy the space between the two CE and complete the basal development of the *septum primum*. Of the three structures that make up the AVMC, only the DMP undergoes a process of partial mesenchymal-muscular differentiation[50]. From this transformation of the DMP into muscle tissue, the ridge of the *fossa ovale* and the muscular lining of the atrial portion of the AV node take shape, to form the so-called transitional cells[4]. The central portion of the DMP does not undergo this "muscularization" process, but forms the tendon of Todaro[3].

The pathogenesis of ASVD has not yet been completely clarified and little attention has been devoted to determining whether there are differences in the development of the various subtypes (partial, intermediate, complete)[3]. With regards to veterinary medicine, there are no specific works on dogs or cats[38]. In the past it was believed that the defect consisted of underdevelopment and lack of fusion of the EC and the condition was, therefore, erroneously defined as "endocardial cushion defect". However, experimental studies on mice have shown that the EC of animals with AVSD are larger than normal and appear to be fused[36,37]. Nowadays, great importance is attributed to perturbations in the development of the DMP and MC (Fig. 12b) in the genesis of atrial and atrioventricular defects, although there are many points of disagreement[42,43]. The only concept on which the scientific community agrees is that, in order for the process of septal formation to occur regularly, the *septum primum* with its MC, the *septum secundum*, the EC and the DMP must develop, interact and merge with one another in a precise spatial-temporal sequence[50,51]. On the basis of murine models, the hypothesis that is currently most accredited[50] is that the pathogenesis of the partial forms of AVSD lies in a genetic disorder involving exclusively the cell population that forms the DMP, deriving from the second heart field. The complete forms, on the other hand, would derive from a disorder that involves not only the DMP, but also the cells forming the CE and the ventricular myocardium. This work describes a case of partial AVSD in a cat. The clinical, echocardiographic and anatomo-pathological features are in line with those of the few cases described in the veterinary literature.

A regular process of septal formation requires that the *septum primum* with its mesenchymal cap, the *septum secundum*, endocardial cushions and the dorsal mesenchymal protrusion interact with each other in a precise spatial-temporal sequence.

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KEY POINTS

- Atrioventricular septal defect (AVSD) is a complex congenital heart disease caused by abnormal development of the atrioventricular junction.
- A decisive contribution to the formation of this area, which anatomically and functionally separates the atria from the ventricles, is made by the atrioventricular mesenchymal complex (AVMC), which consists of the mesenchymal cap (MC), endocardial cushions (EC), dorsal mesenchymal protrusion (DMP) and *septum secundum*.
- The abnormal growth of this area of the heart leads to an alteration of the normal anatomy of the septa, of the atrioventricular valves and of the electrophysiology of the conduction system.
- AVSD can be distinguished into complete, partial and intermediate forms.
- Echocardiography is a decisive investigation for making an *in vivo* diagnosis of AVSD.

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