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Short title

Double outlet right ventricle in small animals

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Abstract

This report describes five cases of double outlet right ventricle (DORV) in four dogs (3 to 18 months old; two males and two females) and a domestic shorthair cat (6-month-old, female) presented with various clinical signs including tachypnea (n=5), exercise intolerance (n=5), mucous cyanosis (n=3), delayed growth (n=2) and/or lethargy (n=2). The represented canine breeds were Poodle, Yorkshire Terrier, Samoyed, and Shetland Sheepdog.

For all animals, echocardiography revealed marked aortic dextroposition with both arterial trunks totally arising from the right ventricle, associated with a ventricular septal defect (VSD) and various other congenital abnormalities, including subvalvular aortic stenosis (n=2), minor aortic insufficiency (n=5), subvalvular pulmonic stenosis with pulmonary trunk hypoplasia (n=1), patent ductus arteriosus (n=1), minor mitral and/or tricuspid dysplasia (n=3). Subsequent cardiac remodeling was characterized by marked right ventricular hypertrophy for all patients, associated with right ventricular and right atrial dilation for most of them (4/5).

Two dogs died soon after the initial DORV diagnosis (i.e., after 24 hours and two months). A surgical correction attempted for another dog confirmed the presence of a DORV associated with patent ductus arteriosus, but the animal died during the procedure from sudden cardiac arrest. The fourth dog underwent a contrast-enhanced retrospective electrocardiogram-gated multidetector computed tomography angiography under general anesthesia, which confirmed the conotruncal malformation. Despite episodes of exercise intolerance, this dog is still alive, at the age of 48 months, as is the cat at the age of 16 months.

Key words: Canine; Congenital; Doppler; Feline; Heart

57 **Abbreviations**

bpm	beats per minute
CT	computed tomography
DORV	double outlet right ventricle
ECG	electrocardiographic
LV	left ventricle
LVPWs	left ventricular posterior wall thickness at end-systole
PCV	packed cell volume
RA	right atrium
RBC	red blood cells
RV	right ventricle
RVFWs	right ventricular free wall at end-systole
RVDd	right ventricular dimension at end-diastole
TGA	transposition of the great arteries
VSD	ventricular septal defect

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Case 1

A 17-month-old male Poodle dog, weighing 5.0 kg, was referred to the Alfort Cardiology Unit (UCA) at the Veterinary Hospital (CHUVA) of the Alfort National Veterinary School (ENVA) for exercise intolerance and intermittent tachypnea, which had both worsened over the past three months. The physical examination showed congested mucous membranes and a grade I/VI right basilar systolic heart murmur.

Two- and three-dimensional echocardiographic examination[d] coupled with color- and continuous-wave Doppler modes (Figs. 1A and 1B), revealed a large doubly committed ventricular septal defect (VSD; maximal diameter: 16 mm) characterized by an intermittent bilateral low-velocity shunt (left-to-right in systole and right-to-left in early-diastole, with a maximal velocity of 1.1 and 0.9 m/s respectively, and absent at end-diastole). Severe aorta dextroposition was also observed, with the aorta entirely originating from the right ventricle. Minor aortic insufficiency was also noted. Based on these echocardiographic findings, the dog was diagnosed with double outlet right ventricle (DORV). The peak systolic transpulmonary flow velocity assessed using continuous-wave Doppler mode was 2.0 m/s. End-systolic right ventricular free wall and left ventricular posterior wall thicknesses (RVFWs and LVPWs, respectively) were measured using the two-dimensional guided M-mode from the right parasternal ventricular short-axis view, and confirmed marked right ventricular (RV) wall thickening (RVFWs:LVPWs ratio = 130%, reference interval: 24-50%, [1]), associated with RV dilation (RV end-diastolic diameter (RVDd) to left ventricular end-diastolic diameter ratio of 79%, reference interval: 7-33% [1]), and a paradoxical septal motion. The right atrium (RA) was also markedly dilated, with a right to left atrium ratio (measured at end-diastole at the level of the atrioventricular valves using the right parasternal 4-chamber view) of 1.4 (reference range: 0.6-1.0 [2]). The caudal

vena cava was unremarkable. Minor mitral and tricuspid insufficiencies, associated with mild leaflet remodeling, were also observed. Concomitant electrocardiographic (ECG) tracing showed a normal sinus rhythm with right axis deviation (heart rate between 80 and 100 beats per minute (bpm)).

To better describe the cardiac and vessels malformations, a contrast-enhanced multidetector computed tomography (CT) angiography with retrospective ECG-gated reconstructions[e,f] was subsequently performed under general anesthesia (Figs. 1C and 1D; Videos 1 to 3). This confirmed the association of severe aortic dextroposition and a large doubly committed VSD, with secondary marked RA and RV dilation associated with RV hypertrophy. A subpulmonary infundibulum was observed without any subaortic infundibulum. An aberrant coronary artery emerging from the pulmonary trunk was also detected (Fig. 1D). Hematology revealed mild polycythemia (red blood cells (RBC) = 8.9 x 10^{12}/L, reference range: 5.5-8.5 x 10^{12}/L; hemoglobin = 21.3 g/dL, reference range: 10.0-18.0 g/L; packed cell volume (PCV) = 55.2%, reference range: 35.0-55.0%). Biochemistry was unremarkable.

An oral medical treatment (spironolactone[g] 0.5 mg/kg/day and omega-3 fatty acids[h]) was prescribed. At the time of writing, this dog is still alive at the age of 48 months and appears in good physical condition, despite some episodes of exercise intolerance.

Case 2

A 1.5-year-old female Yorkshire Terrier dog, weighing 3.9 kg, was referred for chronic seizures, which had intensified over the previous week. Episodes of weakness, exercise intolerance and dyspnea had been reported since birth. An oral medical treatment that included benazepril[i] 0.3 mg/kg/day and spironolactone[g] 1.3

mg/kg/day with furosemide[j] (1.3 mg/kg) in the case of dyspnea, was prescribed at 2 months of age by the referral veterinarian,

Upon admission, the animal was lethargic, cyanotic and tachypneic. Cardiac auscultation revealed a grade V/VI right mediothoracic systolic heart murmur and a grade IV/VI left basilar systolic heart murmur.

Two-dimensional and Doppler echocardiography[d] led to diagnosis of a DORV characterized by an aorta emerging entirely from the RV, along with a small (3.7 mm) non-committed muscular VSD, causing a left-to-right shunt (peak velocity of 5.6 m/s; Figs. 2A and 2B). A subpulmonary infundibulum was clearly observed without any subaortic infundibulum. The pulmonic flow assessed using color-flow Doppler mode was laminar. Conversely, the aortic flow was turbulent and showed an increased peak velocity (5.52 m/s; peak systolic pressure gradient = 126 mmHg) due to the presence of subvalvular aortic stenosis, with concomitant mild aortic insufficiency. Right ventricular hypertrophy (RVFWs:LVPWs ratio = 81% [1]), along with left ventricular (LV) hypertrophy and a secondary decrease of LV internal diameters, were also noted (normalized LV end-diastolic and end-systolic internal diameters of 1.0 and 0.7 [3]). Dilation of the pulmonary trunk, associated with a “notched” Doppler flow pattern of the pulmonary artery flow and decreased peak systolic transpulmonary flow velocity (0.49 m/s [4,5]), suggestive of pulmonary arterial hypertension, were also observed. Concomitant ECG tracing displayed a sinus rhythm without any significant abnormality (heart rate between 90 and 110 bpm).

Complete blood count revealed severe polycythemia (RBC = 12.09 x 10^{12}/L and PCV = 84%). The dog died suddenly 24 hours after diagnosis.

The postmortem examination (Fig. 2C) confirmed the presence of all the echocardiographic abnormalities (DORV, VSD and subvalvular aortic stenosis).

Histopathological examination of the lungs (Fig. 2D) revealed severe remodeling of the pulmonary arteries, with plexiform arterial networks, hypertrophy of the media, intimal fibrosis and thrombosis, all of which were consistent with chronic pulmonary arterial hypertension.

Case 3

A 4-month-old male Samoyed puppy (8.1 kg) was referred for exercise intolerance, lethargy, shortness of breath, mucous cyanosis, and occasional coughing, that had worsened over the last two weeks.

On presentation, the main physical examination findings included tachypnea with mild mucous cyanosis and delayed growth. Cardiac auscultation revealed a grade II/VI right mediothoracic systolic murmur and a grade II/VI left basilar diastolic murmur.

Two- and three-dimensional echocardiographic examination, coupled with color-flow Doppler mode (Fig. 3A),[d] revealed a DORV, with complete aorta dextroposition associated with mild aortic insufficiency. A subpulmonary infundibulum was clearly observed without any subaortic infundibulum. The peak systolic transpulmonary flow velocity assessed using continuous-wave Doppler mode was 1.4 m/s. A large perimembranous subaortic VSD (up to 1.4 cm) with bilateral low-velocity shunt (mostly left-to-right: 1.69 m/s, gradient = 11 mmHg) was also observed. The RV was severely hypertrophied and dilated (RVFWs:LVPWs ratio = 206%; RVDd to LV end-diastolic diameter ratio = 103% [1]), leading to a paradoxical septal motion and remarkably decreased LV diameters (normalized LV end-diastolic and end-systolic internal diameters of 0.9 and 0.6, respectively [3]). The RA was also markedly dilated (right to left atrium ratio = 1.8 [2]), with secondary dilation of the caudal vena cava.

The pulmonary trunk and RV outflow tract were also dilated. A high velocity pulmonary insufficiency was observed (4.41 m/s at end-diastole, gradient = 78 mmHg), suggesting the presence of severe diastolic pulmonary arterial hypertension. Additionally, using color-flow Doppler mode from the right parasternal transaortic short-axis view, an ascending non-aliased low velocity flow was visualized within the pulmonary trunk, consistent with a patent ductus arteriosus providing a left-to-right low velocity shunt (Fig. 3B). Lastly, a mild mitral insufficiency accounting for minor mitral dysplasia, was found. The concurrent electrocardiogram showed a sinus rhythm with right axis deviation (heart rate between 130 and 175 bpm). The PCV was 54%.

Spironolactone[g] (1.2 mg/kg/day per os) was initially prescribed. A surgical correction under cardiopulmonary bypass was planned with the main objective to suture a patch in order to isolate the connection between the aorta to the LV while leaving the pulmonary trunk connected to the RV. Unfortunately, the patient died when starting cardiopulmonary bypass owing to ventricular fibrillation. The view of the open heart confirmed a DORV associated with a subaortic VSD and a patent ductus arteriosus. A histopathological examination was declined by the owners.

Case 4

A 3-month-old female Shetland Sheepdog (5.5 kg) was referred for suspected congenital heart disease. The owners reported exercise intolerance and mucous cyanosis. Physical examination findings included delayed growth, mucous cyanosis, tachypnea, and grade IV/VI left basilar systolic heart murmur.

Two-dimensional and Doppler echocardiography[d] was subsequently performed and revealed a DORV, with the aorta emerging completely from the RV without any well-

184 defined subaortic infundibulum. A severe subvalvular aortic stenosis was also
185 observed (trans-stenotic peak pressure gradient = 127 mmHg) with mild aortic
186 insufficiency. A small-diameter (3.1 mm) subaortic VSD, leading to a bidirectional
187 interventricular shunt, was also noted. Assessment of the pulmonary outflow tract
188 revealed pulmonary trunk hypoplasia, associated with severe infundibular pulmonary
189 stenosis (peak systolic transpulmonary flow velocity assessed using continuous-
190 wave Doppler mode = 6.4 m/s; trans-stenotic peak pressure gradient = 165 mmHg).
191 Consequently, the RV was severely hypertrophied and dilated (RVFWs:LVPWs ratio
192 = 169%; RVDd to LV end-diastolic diameter ratio = 89% [1]), as was the RA (right to
193 left atrium ratio = 1.4 [2]). Hypertrophy of the interventricular septum was also
194 observed, as well as decreased LV internal diameters (normalized LV end-diastolic
195 and end-systolic internal diameters of 0.8 and 0.3, respectively [3]). Minor mitral
196 insufficiency resulting from mild leaflet remodeling was also found. The concomitant
197 electrocardiogram showed a respiratory sinus arrhythmia (heart rate between 90 and
198 120 bpm). Hematology confirmed polycythemia (RBC = 9.82 x 10^{12}/L; PCV = 74%).
199 No medication was prescribed according to the owner's request. The animal died
200 suddenly at home two months after the initial diagnosis, and no necropsy could be
201 performed.
202
203 **Case 5**
204 A 6-month-old 2.5 kg domestic shorthair female cat was referred for exercise
205 intolerance and episodic dyspnea. The cat exhibited tachypnea after minimal manual
206 restraint, and auscultation revealed a grade IV/VI right mediothoracic systolic heart
207 murmur.

Transthoracic echocardiography was subsequently performed,[d] and confirmed that the aorta emerged entirely from the RV and was even located on the right side of the pulmonary trunk (Figs. 4A and B). A short bilateral infundibulum emerging from the RV was seen. A large muscular VSD (Fig. 4C) mainly committed with the pulmonary trunk was also found, so that the LV ejection flow passed through the VSD towards both arteries, but mostly into the pulmonary trunk. A mild aortic insufficiency was detected. The peak systolic transpulmonary flow velocity assessed using continuous-was Doppler mode was 1.3 m/s. A pulmonary insufficiency of high velocity (3.14 m/s) was also present suggesting diastolic pulmonary arterial hypertension. Accordingly, the RV was both hypertrophied and dilated, with a mild RA dilation. The interventricular flow was mostly left-to-right and was characterized by a low peak velocity (1.2 m/s), indicating a very low-pressure gradient (6 mmHg) owing to high RV systolic pressure, and was rarely right-to-left at end systole and early diastole. Concomitant ECG tracing showed a normal sinus rhythm (150 bpm) along with right axis deviation. Hematology confirmed polycythemia (RBC = 9.82 x 10^{12}/L; PCV = 74%). A cardiac CT scan was proposed but the owner preferred a more conservative approach and consented only to medical palliation. This consisted of spironolactone[g] (1 mg/kg/day). The cat is still alive at the age of 16 months and the owners report an improvement of tachypnea.

Discussion

Double outlet right ventricle is a congenital heart disease encompassing a wide spectrum of anatomic abnormalities and pathophysiologic disturbances, explaining many controversies in human cardiology regarding its definition, nomenclature, and

classification as well as optimal timing for surgical repair [6]. According to the consensus definition issued by the *Congenital Heart Surgery Nomenclature and Database Project*, DORV is a rare conotruncal anomaly corresponding to a particular ventriculo-arterial connection, in which the two arterial trunks emerge entirely or predominantly from the RV [6]. In most cases, viability is provided by the presence of a VSD associated with various structural connections to both arteries and allowing blood to flow from the LV to the RV, and then into the pulmonary and systemic circulations. In humans, DORV only accounts for approximately 1 to 3% of congenital cardiac defects [7]. Veterinary retrospective studies suggest that DORV is also a rare congenital malformation in both cats and dogs, accounting for 0.5% to 1% of congenital cardiac defects in cats [8,9], with no DORV cases in retrospective reviews performed on 105 to 976 dogs with congenital heart diseases [8,10,11]. A few isolated case reports, relying essentially on postmortem examinations, have documented this condition in dogs and cats [12-15], horses [16,17], alpacas [18] and calves [19,20]. To the best of our knowledge, the present report is the first case series with an antemortem DORV diagnosis in small animals, i.e., four dogs and one cat. In all five animals, the echocardiographic diagnosis of DORV was based on the presence of a VSD associated with complete commitment of the aorta to the RV, which could be confirmed by CT scan (Case 1) and by necropsy in two cases (Cases 2 and 3). The diagnosis of DORV in Cases 4 and 5 was solely based on echocardiography, which represents a limitation of the present report.

The first DORV description was done in 1898, but the term “DORV” was not introduced until 1957, as the defect was initially considered as a particular form of transposition of the great arteries (TGA) [21]. The double outlet left ventricle, another abnormal type of ventriculoarterial connection in which both great arteries arise

entirely or predominantly from the LV, was then described several years later [22]. In humans, DORV is a complex cardiac malformation characterized by great heterogeneity among affected patients, depending on the VSD characteristics, the spatial relationship between the VSD and the arterial trunks and between the arterial trunks themselves, and the presence or absence of pulmonic or aortic stenosis, and of other concomitant malformations [6,7,23]. The VSD characteristics include its restrictive or unrestrictive features and also its location, with subaortic VSD being the most common type in human patients with DORV, accounting for approximately 50% of surgical patients [6]. Thus, as illustrated in the present case series, DORV encompasses a wide spectrum of anatomic defects, with a great variability of clinical presentations and pathophysiologic features, including extreme forms mimicking either tetralogy of Fallot or TGA in the case of respectively associated pulmonic stenosis and subpulmonary VSD [6,23]. Various classifications of DORV taking into account these anatomic variations have been proposed in an attempt to standardize surgical approaches in human patients [6,23,24]. One of the most commonly used DORV classification systems identifies four DORV types, i.e., the VSD type (including DORV with subaortic or doubly-committed VSD and without pulmonic stenosis), the tetralogy of Fallot type (including DORV with subaortic or doubly-committed VSD and pulmonic stenosis), the TGA type (including DORV with subpulmonary VSD) and the remote VSD type characterized by a non-committed VSD (i.e., a VSD distant from the arterial trunks, observed in the muscular interventricular septum) [6]. According to this classification, two DORV types were diagnosed in the present report, and confirmed by either necropsy or CT scan, i.e., two VSD types for Cases 1 and 3 (characterized by a doubly-committed or subaortic VSD in the absence of pulmonic stenosis) and one remote VSD type for Case 2. Case 4 can be classified as a

tetralogy of Fallot type DORV, owing to the concomitant presence of severe infundibular pulmonary stenosis, and Case 5 as a TGA type owing to the echocardiographic visualization of a large muscular subpulmonary VSD. However, since the latter two descriptions were limited to echocardiographic examinations, the exact location of the VSD, especially for Case 5, could not be confirmed with certainty.

Beside its above-mentioned extreme anatomic variability, DORV in human patients is also characterized by its common association with multiple cardiac malformations [6,25]. In this context, CT scan has been shown to be an excellent diagnostic tool for detecting DORV-associated malformations, and a combination of transthoracic echocardiography with CT scan allows excellent diagnostic performance (100 % sensitivity for detecting intracardiac anomalies *versus* 91% for echocardiography alone) [25]. Only one dog in the present case series was able to benefit from these combined imaging techniques (Case 1), as the other dogs were presented before acquisition of the CT-scan technique in our facility, while the cat's owners declined the investigation. Nevertheless, various congenital abnormalities were found associated with DORV in all the animals, including subvalvular aortic stenosis (n=2), aortic insufficiency (n=5), subvalvular pulmonic stenosis with pulmonary trunk hypoplasia (n=1), patent ductus arteriosus (n=1), and minor atrioventricular dysplasia (n=3). Understandably, the variety of both the anatomic DORV phenotypes and associated malformations explains the wide range of clinical presentations, as illustrated in the present report.

In conclusion, this short case series illustrates the wide spectrum of congenital anatomic anomalies, associated defects, and clinical presentations embodied by

DORV in small animals. Echocardiography remains adequate to reach a diagnosis. However, owing to the complexity and heterogeneity of DORV, a cardiac CT scan appears to be a wise option before attempting any surgical approach.

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Footnotes

[d] Vivid 7, Vivid E9; General Electric Medical System, Waukesha, WI, USA.

[e] Brilliance 64-slice CT scanner, Philips Medical Systems, Cleveland, OH, USA.

[f] 3mensio, PIE Medical Imaging, Maastricht, The Netherlands.

[g] Prilactone, CEVA, Libourne, France.

[h] Agepi Oméga 3, MP Labo, Grasse, France.

[i] Nelio, CEVA, Libourne, France.

[j] Dimazon, Intervet, Beaucouze, France.

Figure legends

Figure 1: Representative color-flow Doppler (A, B) and three-dimensional retrospective ECG-gated (phase 30%) computed tomography (CT) reconstruction of the heart and great vessels (C and D) from a 17-month-old Poodle dog with double outlet right ventricle (Case 1).

A and B - Color-flow Doppler images obtained from the right parasternal 5-chamber view confirming a left-to-right shunt through the ventricular septal defect during the early systolic phase (A) and the presence of right ventricle-aortic flow during the whole systolic phase (B)

C - This CT image confirms a large ventricular septal defect (VSD) with the aorta exiting from the hypertrophied right ventricle.

D – Note on this CT image the presence of an aberrant coronary artery exiting from the pulmonary trunk.

Ao: aorta; LA: left atrium; LV: left ventricle; RV: right ventricle.

Figure 2: Images from a 1.5-year-old Yorkshire Terrier dog diagnosed with double outlet right ventricle (Case 2).

A and B - Two-dimensional (A) and color-flow-Doppler mode (B) images respectively obtained from the right parasternal transaortic short-axis view and a right parasternal long-axis view, showing that both arteries arise from the right ventricle. Other abnormalities (B) include a turbulent left-to-right shunt through a small-sized defect within the muscular part of the interventricular septum and a subaortic stenosis (white arrows). The connection between the right ventricle and the aorta is show by an asterisk in both figures.

C - Necropsy examination (after oblique incision of the right ventricle) confirming that

the aorta and the pulmonary trunk both emerge from the right ventricle. Note also the small muscular non-committed ventricular septal defect (arrow).

D - Histopathological examination showing a major remodeling of the pulmonary arteries with marked obliterative muscular hypertrophy (arrow) and intimal thickening. These plexiform lesions are consistent with pulmonary arteriopathy due to severe pulmonary arterial hypertension. Hematoxylin, eosin and saffron stain (Anatomical Pathology department, BioPôle Alfort, Ecole Nationale Vétérinaire d'Alfort)

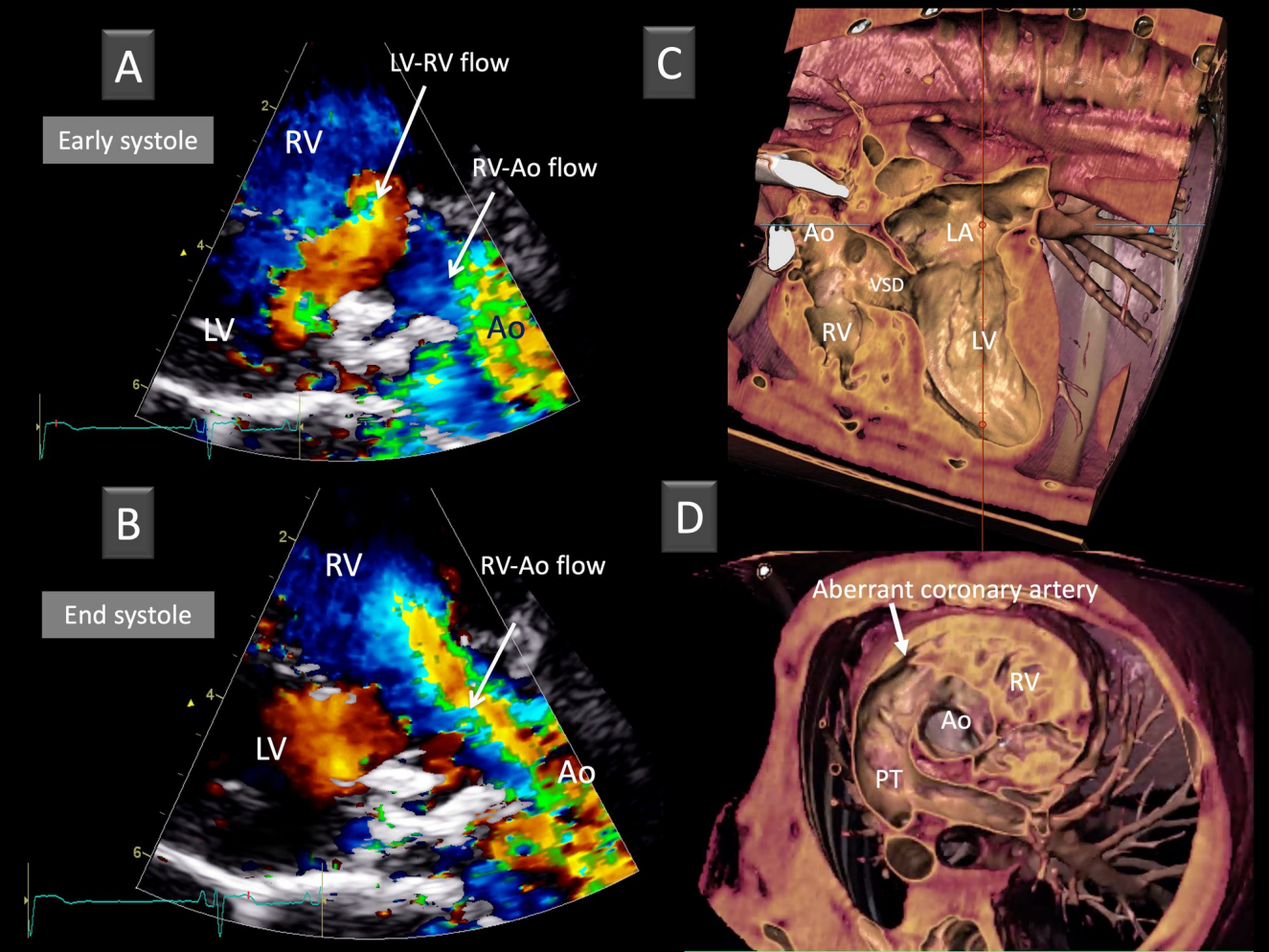
Ao: aorta; LA: left atrium; LVPW: left ventricular posterior wall; PT: pulmonary trunk; RA: right atrium; RV: right ventricle; RVW: right ventricular wall; VSD: ventricular septal defect.

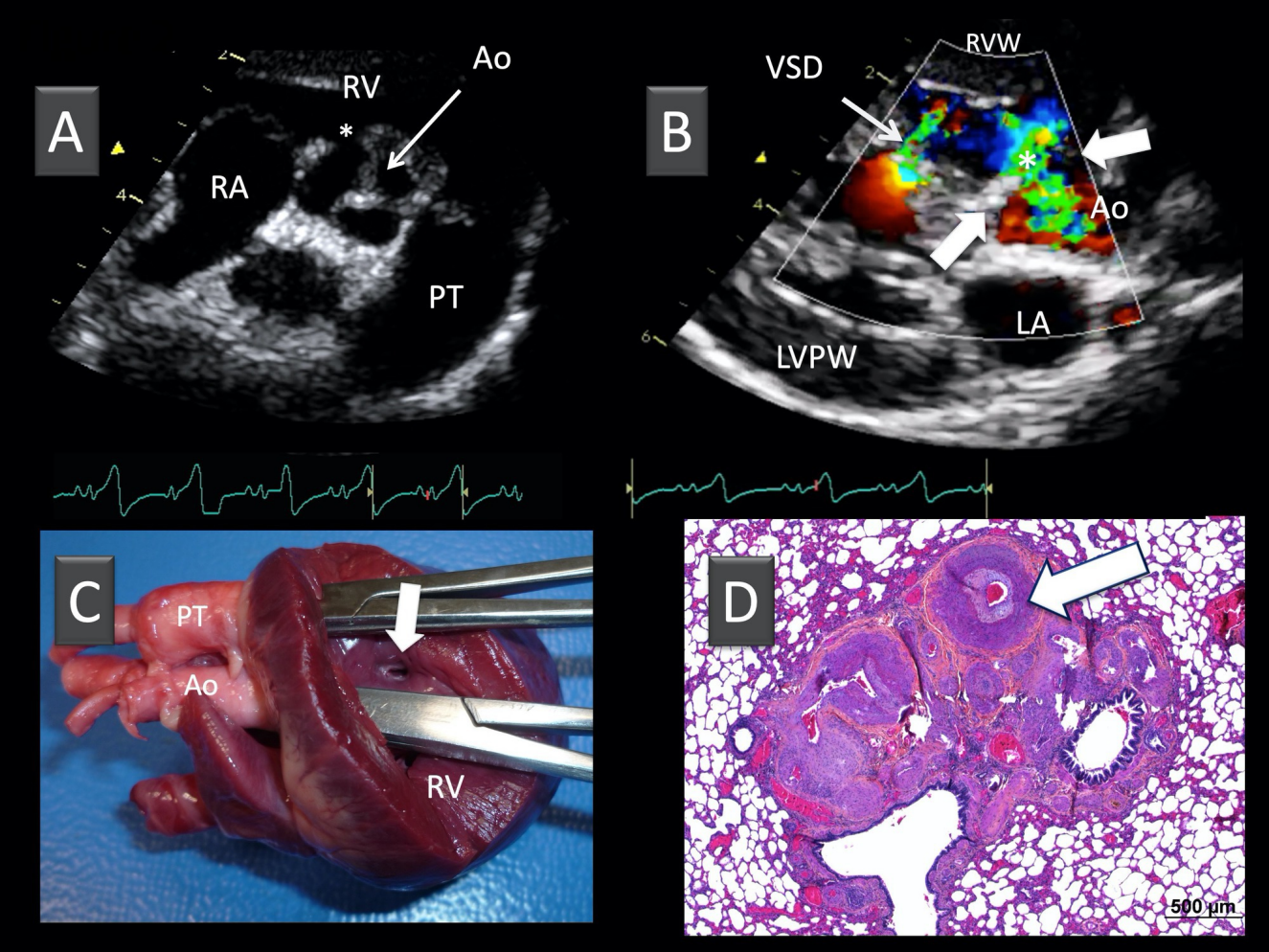
Figure 3: Two-dimensional (A) and color-flow-Doppler mode (B) images recorded in a 4-month-old male Samoyed dog diagnosed with double outlet right ventricle (Case 3), respectively from the right parasternal 5-chamber view and the right parasternal transaortic short-axis view. Both images confirm that the aorta arises from the right ventricle. Figure 3A additionally shows a large ventricular septal defect (arrow) and Figure 3B a non-aliased ascending flow within the pulmonary trunk (arrow) owing to the presence of a patent ductus arteriosus.

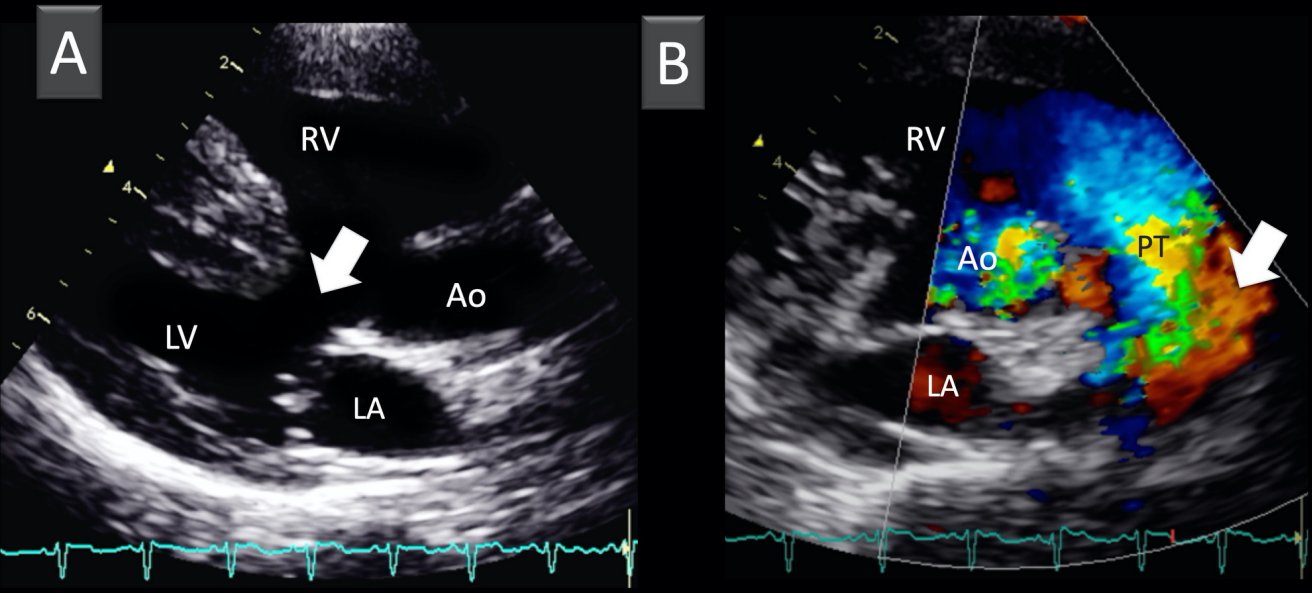
Ao: aorta; LA: left atrium; LV: left ventricle; PT: pulmonary trunk; RV: right ventricle.

Figure 4: Two-dimensional (A) and color-flow Doppler mode (B and C) systolic images recorded in a 6-month-old female cat diagnosed with double outlet right ventricle (Case 5), obtained from a left cranial parasternal short-axis view (A) and two right parasternal long-axis views (B and C). Note the abnormal right lateral position of the aorta (A and B) and the systolic left-to-right shunt through a

448 large defect within the interventricular septum (C). The larger diameter of the
449 pulmonary trunk, as compared with that of the aorta, may be due to the increased
450 flow coming from the ventricular septal defect.
451 Ao: aorta; LA: left atrium; LV: left ventricle; PT: pulmonary trunk; RA: right atrium; RV:
452 right ventricle; RVW: right ventricular wall.
453


A
Early systole
LV-RV flow
RV-Ao flow
RV
LV
Ao
B
End systole
RV
RV-Ao flow
LV
Ao
C
Ao
LA
VSD
RV
LV
D
Aberrant coronary artery
RV
Ao
PT


A
RV
Ao
*
RA
PT
B
VSD
RVW
*
Ao
LA
LVPW
C
PT
Ao
RV
D
500 µm


A
RV
Ao
LV
LA
B
RV
Ao
PT
LA

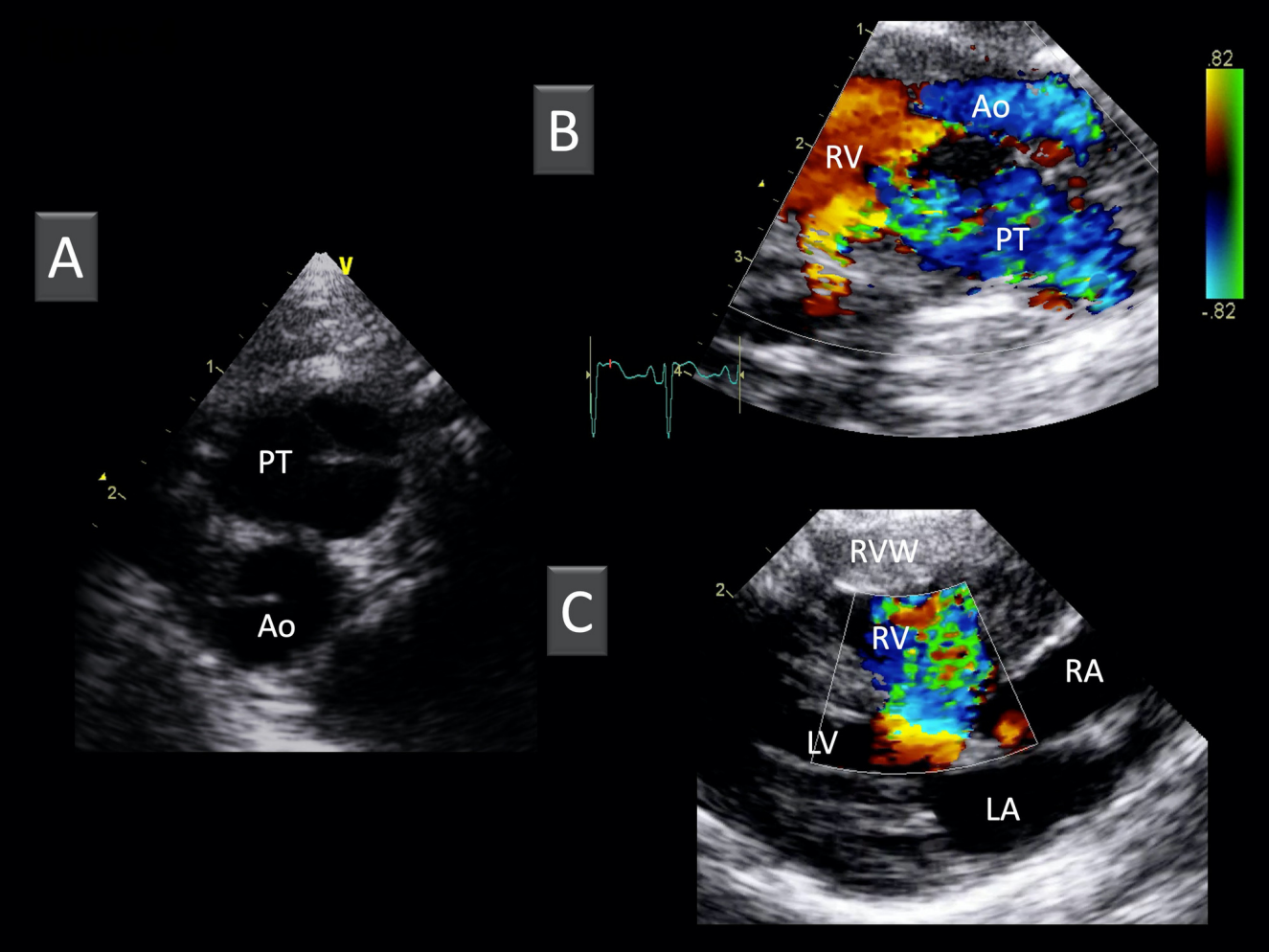

A
PT
Ao
B
RV
Ao
PT
.82
-.82
C
RVW
RV
RA
LV
LA

Table 1: Video captions

Video number	Description
Video 1	Contrast-enhanced retrospective ECG-gated multidetector computed tomography scan with two- and three-dimensional orthogonal views showing the large ventricular septal defect and the aorta emerging from the right ventricle. The aberrant coronary artery exiting from the pulmonary trunk is also seen in the two movies on the left.
Video 2	Contrast-enhanced retrospective ECG-gated multidetector computed tomography scan with two- and three-dimensional orthogonal views showing the aorta and the pulmonary trunk both emerging from the right ventricle, with an aberrant coronary artery from the pulmonary trunk. Note the absence of left ventricular outflow track.
Video 3	Contrast-enhanced retrospective ECG-gated multidetector computed tomography scan: volume rendering video.