ABDOMINAL AORTIC FLOW IN DOGS WITH PATENT DUCTUS ARTERIOSUS

Master Thesis Medicine of Companion Animals; Utrecht University

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Abstract

Patent ductus arteriosus (PDA) is a condition seen both in dogs and humans. In dogs there is a histological abnormality, which causes an inability for the ductus to close. In humans, there is a relationship between preterm birth and the occurrence of PDA. This condition can eventually lead to congestive heart failure. Diagnosis is through echocardiography. In humans, only hemodynamic significant PDAs (hsPDA) are closed. The hemodynamic significance of a PDA is assessed through echocardiography. Besides the conventional echocardiographic measurements, the flow in the descending aorta is measured. Absent or retrograde diastolic flow is an additional sign for a hsPDA. To our knowledge this is not yet researched in dogs. The aim of this study is to determine if the ultrasonographic assessment of the diastolic flow in the abdominal descending aorta is feasible in dogs, and if the abnormalities described in humans can be observed in dogs with PDA, when the condition is considered hemodynamically significant based on echocardiography.

In this prospective study, ten dogs diagnosed with a left-to-right shunting PDA through echocardiography were included. A control group was created, consisting of ten subjects including healthy dogs, dogs with congenital heart diseases other than PDA, and dogs with PDA after ductal closure. The dogs in both groups received an echocardiographic examination and the flow in the abdominal aorta was assessed.

In the PDA group, two dogs had no evidence of cardiac enlargement on echocardiography and were categorized as having a non-hsPDA. One of them had normal abdominal aortic flow, while the other had absent end-diastolic flow. Of the eight dogs with hsPDA, five dogs had retrograde flow, one dog had a normal flow pattern, and one dog had an alternating pattern between retrograde flow, absent end-diastolic flow and normal flow. This flow was concluded as abnormal. In one dog, a filter of velocity on ultrasound was used to filter the low velocities. Because of this, the image was deemed to be of insufficient quality for assessment. All dogs in the control group had normal flow in the abdominal aorta.

The small sample sizes should be a reason for caution when interpreting the results, but the following (preliminary) conclusions can be drawn: firstly, the use of ultrasound to assess the flow in the abdominal aorta is feasible, providing low velocities are filtered adequately. Secondly, the presence of absent or retrograde flow in the descending aorta in humans with hsPDA, is also seen in dogs with hsPDA in the abdominal aorta, and not in the control group in dogs without PDA. So, the detection of absent or retrograde diastolic flow seems a strong indicator of hsPDA. Further research is necessary and confirming the diagnostic power of such a non-invasive, animal-friendly approach, seems of substantial value.

Introduction

The ductus arteriosus (DA) is a vessel that connects the pulmonary artery and the descending aorta in the fetal heart. This structure closes spontaneously in most individuals after birth. When it remains patent after birth, it is abnormal and characterizes a condition named patent ductus arteriosus (PDA). [1]
This condition is among the three most common congenital cardiovascular abnormalities in dogs. [2,3] In humans, there is a correlation between preterm birth and the occurrence of PDA. This is due to physiological aspects that are related to prematurity rather than inherited abnormalities of the ductus. [1] In dogs with PDA, there is a histological abnormality, [4] as discussed below in detail.

When a PDA is present, blood will shunt through the DA from the descending aorta to the pulmonary artery. [1,4] If the resistance in the pulmonary artery is higher than in the aorta, it can also shunt from the pulmonary artery to the aorta, which is called a right-to-left shunting PDA. [1,5]
In subjects with a left-to-right shunting PDA, left-sided congestive heart failure (CHF) can develop. This is due to a volume overload in the pulmonary system and left cardiac chambers, which causes dilation of the pulmonary artery, left atrium, and left ventricle. As a result of the chronic overload, the left side of the heart will develop eccentric hypertrophy. [1,5] With the declining myocardial function due to eccentric hypertrophy, and the activation of the RAAS system, excess fluid retention can occur and left-sided CHF develops. [6,7] Arrhythmias can also develop. [6]

Diagnosis of the PDA is initially made by auscultation, which should reveal, in case of a left-to-right shunting PDA, a continuous “machinery” murmur. To confirm the diagnosis, echocardiography with color-flow Doppler imaging can be used to show a high-velocity, turbulent and continuous flow in the pulmonary artery as the blood leaves the PDA. [1,5]

Patent Ductus Arteriosus in dogs

70% of the dogs with left-to-right PDA will develop CHF before 12 months of age, when no treatment is started. [5] The ductal wall in dogs with PDA is histologically abnormal and contains less smooth muscle, which makes it unable to constrict and close effectively. Normally the DA consists of 98% smooth muscle, with elastic fibers and loose collagen. At the time of closure, the systemic oxygen tension will stimulate the smooth muscle within the DA to constrict, so the DA closes. In dogs with PDA, due to the abnormal formation of the smooth muscle and the elastic tissue, the DA fails to contract efficiently and therefore to close. The smooth muscle is hypoplastic and, secondarily, there is more elastic tissue. A classification system has been developed for histologic grading, as observed in Figure 1. [4]

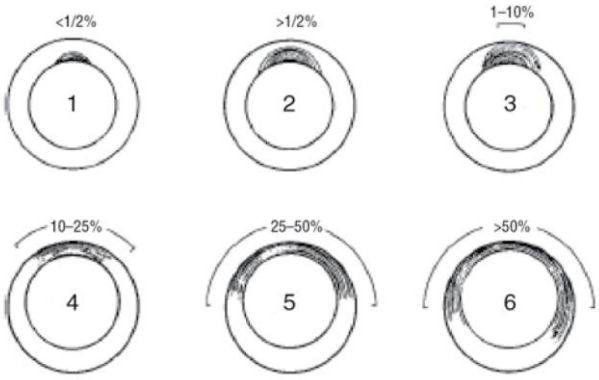

Figure 1. Grading system based on histologic abnormalities of the DA in dogs with PDA. The elastic tissue is represented as a shaded are while the musclular tissue is white. Grade 1 has elastic tissues in less than half of the wall thickness; in grade 2, the elastic tissue extends through more than half of the wall thickness. When the grading increases, the elastic tissue extends through greater percentages of the thickness and cirumference of the PDA, and the muscular (nonshaded) area is progressively smaller. From: Buchanan et al. (2001)

Next to this classification, Buchanan et al. (2001) [4] differentiated the PDA in dogs in four types depending on clinical features, without considering echocardiographic findings. Type 1 is a small asymptomatic PDA, type 2 a medium-sized asymptomatic PDA, but with a mild to moderate left heart enlargement seen on radiographs . Type 3 is a large PDA, further subclassified in 3a and 3b, with type 3a not associated with CHF and type 3b associated with CHF. Type 4 is a large PDA with pulmonary hypertension, leading to right-to-left shunting. With type 1, surgery is not urgent, but it is recommended to achieve a full life span. [4]

Furthermore, Miller et al. (2006) developed an angiographic classification in dogs. [7] Four phenotypes are recognized (Figure 2). Type I PDA progressively tapers from the aorta towards the point of pulmonary insertion and has no abrupt change in ductal diameter. The walls of the PDA form an angle that is typically less than 15 degrees. Type II PDA has an abrupt distal narrowing of more than 50% in ductal diameter. Type II PDA is subdivided in two phenotypes. The subdivision is based on the morphology of the proximal part of the PDA. Type IIA PDA has a constant dimension in the proximal part of de DA, with parallel walls, before abruptly narrowing distally at the insertion point into the pulmonary artery. Type IIB PDA has a conical ductal shape that abruptly narrows at the distal part of the duct, before inserting into the pulmonary artery. The type IIB PDA forms an angle that is between 30^{o} and 60^{o}. Lastly, type III PDA has a tubular appearance and the ductal diameter does not attenuate. [7]

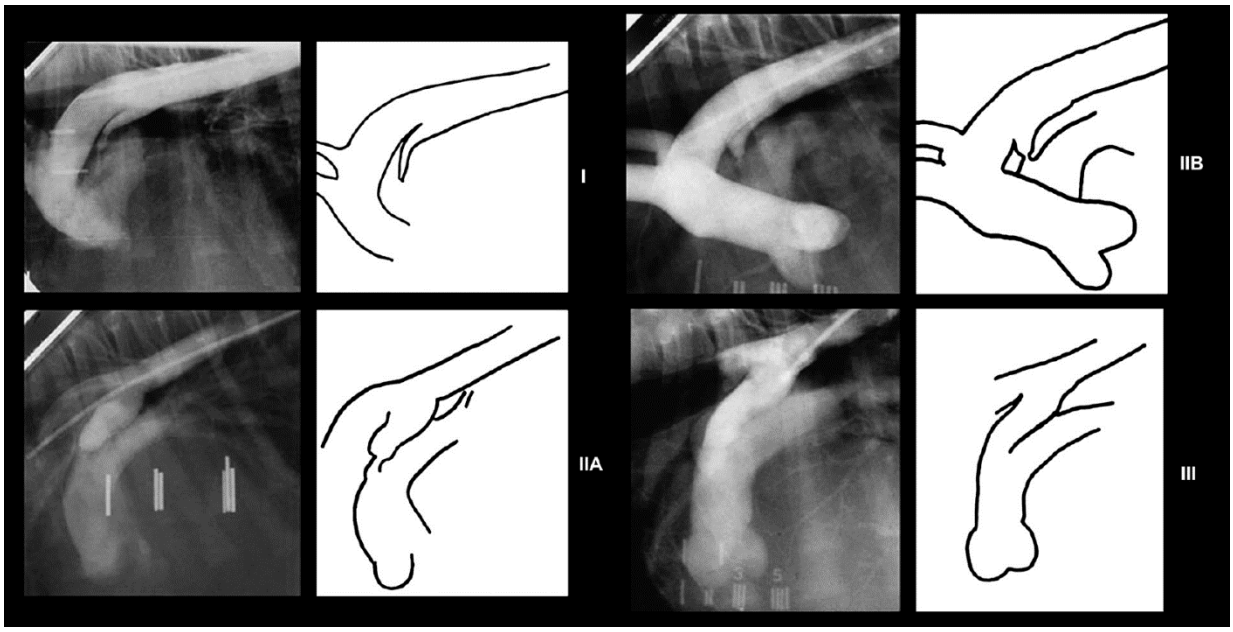

Figure 2. Four types of PDA in dogs based on angiographic appearance. Type I PDA: gradually tapering towards the pulmonary artery. Type IIA PDA: constant dimension with parallel walls that abruptly narrows to the pulmonary artery. Type IIB PDA: conical form. Type III PDA: tubular shape. From: Miller et al. (2006)

Hemodynamic significance of a PDA

To determine if any treatment is necessary in human infants, the hemodynamic significance of a PDA needs to be assessed. PDAs in infants are not always hemodynamically significant. When this is not the case, and the infant does not have comorbidities, no treatment is needed, [8] because there is a high chance of spontaneous closure of the PDA without any treatment [9].

The evaluation of the PDA in humans and in dogs consists of echocardiographic assessment of the morphology of the DA and its size, of the direction of the shunt across the PDA and of the assessment of its hemodynamic significance. [8,10]

To assess if the PDA is hemodynamically significant (hsPDA), the flow ratio of pulmonary flow versus systemic flow (Qp:Qs) is evaluated. In a healthy state, the Qp:Qs is 1. The left ventricular output

reflects the pulmonary blood flow, while the right ventricular output reflects the systemic blood flow. With a hsPDA in preterm infants, the steal phenomenon occurs. The blood flow in the pulmonary artery increases because of the amount of blood that flows from the descending aorta back into the lung circulation through the PDA. Simultaneously, for the same reason, systemic blood flow decreases, causing the Qp:Qs ratio to increase. [8,11,12]

Other echocardiographic markers that can be used to assess the hemodynamic significance of the PDA in infants are the left atrium to aorta ratio, the left ventricular output, and the left pulmonary artery end diastolic output. [13,14] In dogs, the left atrium to aorta ratio, the volume of the left ventricle, the left ventricular internal diameter in diastole, and the pulmonary flow to systemic flow ratio are measurements that can be used. [10]

An additional sign of an hsPDA in infants is absent or retrograde diastolic flow in the descending aorta, which indicates a systemic hypoperfusion. When the flow through the descending aorta is assessed with spectral Doppler in a healthy heart, an anterograde wave is observed in both systole and diastole. The steal phenomenon in PDA will give an absent end diastolic flow or the flow can be retrograde during the whole diastole in more severe cases. With this finding, it is assumed that the systemic perfusion is compromised, thus a hsPDA is present (Figure 3). [8]

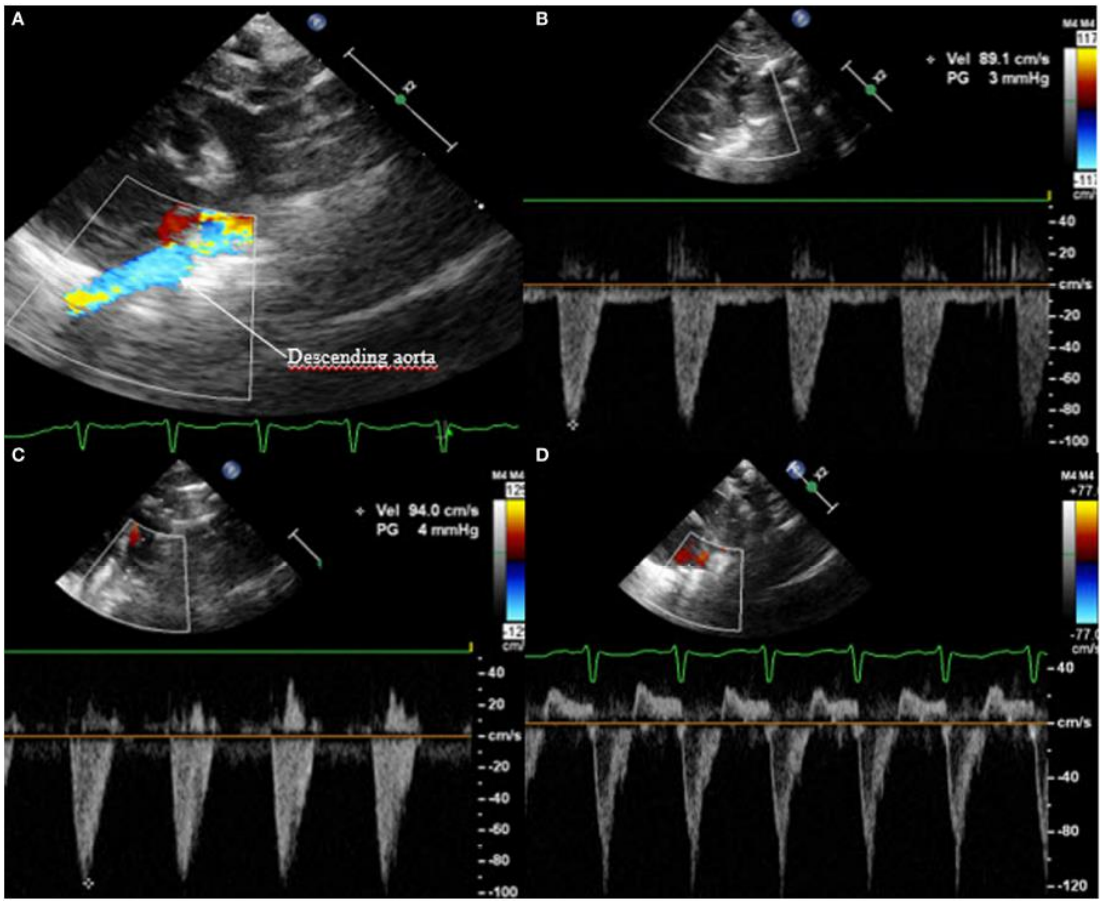

Figure 3. Echocardiographic images of the suprasternal view in human infants. A: Color Doppler of the post ductal descending aorta with (B) a healthy heart with systolic and diastolic anterograde flow, (C) absent end diastolic flow in a heart with PDA, and (D) retrograde flow during the whole diastole in a heart with PDA. From: Arlettaz et al. (2017)

Besides the echocardiographic assessment, the evaluation of a hsPDA also consists of measuring biomarkers in blood, in particular Brain Natriuretic Peptide (BNP) and its inactive N-terminal pro-brain-type natriuretic peptide (NTproBNP). The inactive pro-BNP is released from the ventricle when volume overload is present, which then is cleaved into metabolically active BNP and the inactive

metabolite NTproBNP. These biomarkers increase in neonates when a hsPDA is present. [15] NT-proBNP has also been shown to be elevated in dogs with PDA and correlates with echocardiographic markers as left ventricular internal diameter in systole. [16]

Treatment of the PDA in dogs

The treatment for PDA in dogs consists of closure via catheterization or surgical ligation through thoracotomy. [4,5] Since thoracotomy is an invasive procedure, transvascular catheter techniques were developed to minimize perioperative morbidity. [17] Transvascular PDA occlusion is the treatment method of choice for most veterinary cardiologists, due to a high overall success rate. [18]
The surgical techniques consist of ligating the PDA with suture material or with hemostatic clips. [19]
The catheterization techniques include transarterial or transvenous thrombogenic coil placement in the DA, Amplatz Canine Duct Occluder (ACDO) placement, or a Amplatz Vascular Plug placement. The ACDO is superior to the other minimally invasive devices. It has a low complication rate, as low as 3%. It achieves complete occlusion of the ductal flow in 97.2% of the times. [18] Other studies imply a success rate of 98% to 100%. [20,21]
Following the classification developed by Miller et al. (2006), type I, IIA, and IIB have the possibility to be closed through catheterization. Type III, due to the lack of tapering, does not provide an area where the transvascular occluding device can stay in place. Thus it needs to be ligated surgically. [7,17]
In a study that compared surgical ligation to closure with ACDO, the rate of major complications was higher in surgical ligation than in ADCO placement (respectively 10% and 0%). The rate of survival to hospital discharge was comparable between the two procedures. [22]

Objectives of the study

The assessment of the diastolic flow in the descending aorta is frequently used in preterm infants to determine the hemodynamic significance of a PDA and establish if treatment is needed. [8] To our knowledge, this parameter has not been used in dogs with PDA. This could be related to the difficulties of obtaining a good view of the thoracic descending aorta in dogs. Kirberger et al. (1992) could only get good quality images in 18 out of 50 dogs. [23]

The aim of this study is to determine if the ultrasonographic assessment of the diastolic flow in the abdominal descending aorta is feasible in dogs, and if the abnormalities described in humans can be observed in dogs with PDA, when the condition is considered hemodynamically significant based on echocardiography.

Materials and methods

Animals

In this prospective study, ten dogs of any breed and age diagnosed with a left-to-right shunting PDA through echocardiography were included. Presence of concurrent cardiac or systemic disease, right-to-left shunting through the PDA or CHF represented exclusion criteria.

A control group was also created, and consisted of ten subjects including healthy dogs, dogs with congenital heart diseases other than PDA, and dogs with PDA after ductal closure. Dogs could be of any breed or age. Presence of concurrent cardiac or systemic disease, right-to-left shunting through the PDA or CHF also represented exclusion criteria for this group.

Examination

Client-owned dogs examined at the cardiology department of the Faculty of Veterinary Medicine (Utrecht University, The Netherlands) from April 2021 to December 2021 were included. Furthermore, dogs examined at the private referral center Veterinaire Specialisten (Vught) from October 2021 to December 2021 were included. Inclusion and exclusion criteria are listed above.

Dogs included received an ultrasonographic examination, performed by an EBVS® European specialist in small animal cardiology or a supervised cardiology resident. The investigators were not blinded for ultrasonographic diagnosis when assessing the abdominal aortic flow. All dogs were examined without sedation. The ultrasonographic examinations were performed with commercial ultrasound systems equipped with a 4-10 MHz linear probe.

Measurements in dogs with PDA

First, the presence of a PDA was confirmed and the flow pattern through the PDA was assessed. Then multiple echocardiographic measurements were taken, to assess if a PDA was hemodynamically significant. If at least one of these parameters was abnormal, the PDA was considered to be hemodynamically significant. Then the flow in the abdominal aorta was assessed. The biomarker NT-proBNP was not included as parameter to assess the hemodynamic significance of the PDA.

Confirmation of the PDA and the flow pattern

To confirm the presence of a PDA, color Doppler echocardiography was used in left and right parasternal short-axis views at the level of the pulmonary artery. The Nyquist limit was increased to maximum, and the color intensification close to saturation for the best visualization. The flow measurement was taken at the narrowest point of the turbulent color stream. [24] To measure the velocity of the flow through the DA, continuous wave Doppler was used. The sample volume was placed in the pulmonary artery at the level of the entrance of the duct. This displays a continuous, turbulent, high-velocity flow with a brief interruption during the early systole, due to the systolic flow through the pulmonary artery. Good alignment with the ductal flow should give a peak velocity of > 4m/s, in absence of pulmonary hypertension. [25]

To visualize the DA with two-dimensional echocardiography (2-D) and assess its morphology and dimension, the left or right parasternal transverse heart base view was used. [10]

Left atrium to aorta ratio

The left atrium to aorta ratio (LA:Ao) was measured in right-sided short axis view in end-systole/early ventricular diastole at the aortic valve level with 2-D view. For the aorta (Ao), the first measuring point was placed at the midpoint of the convex curvature of the wall of the right aortic sinus, positioned as close as possible to the blood-tissue border. The second measuring point was positioned at the point where the aortic wall, the noncoronary, and left coronary aortic cusps unite.

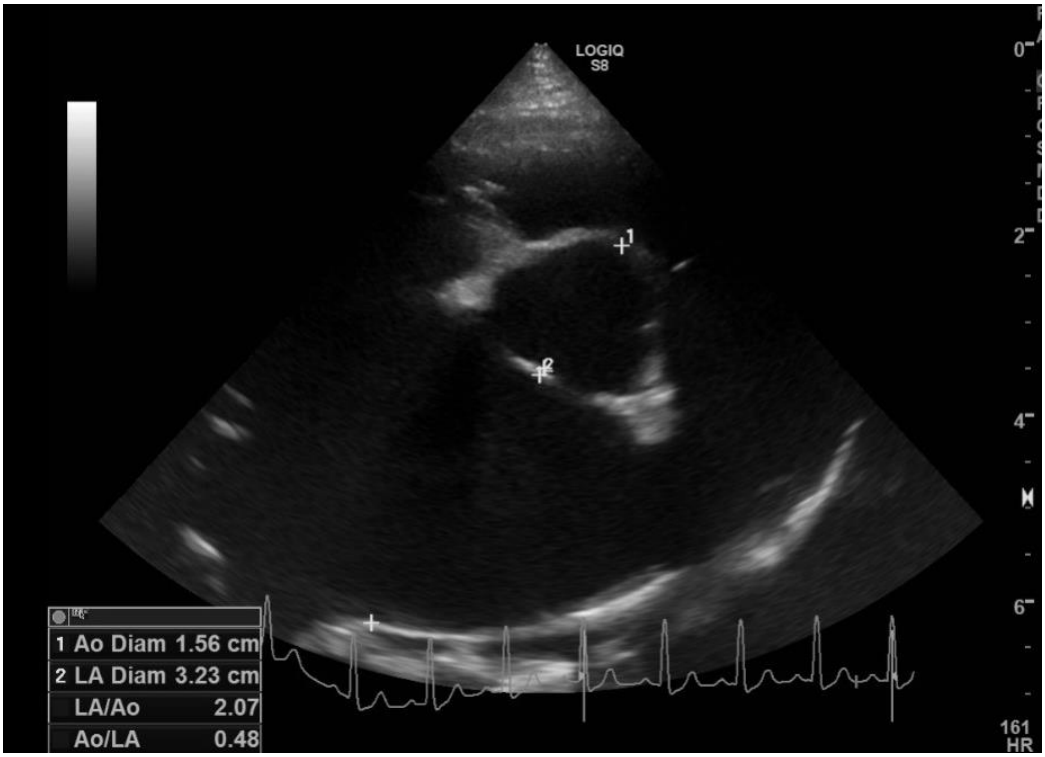

Figure 4 Measurement of the LA:Ao in a dog with PDA and left atrial enlargement. Used with permission of the Small Animal Cardiology Service, Department Clinical Sciences, Utrecht University.

The left atrium (LA) was measured from this point by extending the Ao line to the blood tissue border of the LA wall. [26] The accepted limit of normality used for this parameter is <1.6. [27] See figure 4 for an example.

Left ventricular internal diameter in diastole, normalized for body weight
To measure the left ventricular end diastolic diameter (LVIDd), a 2-D short axis guided M-mode echocardiogram of the left ventricle (LV) in diastole was taken. To calculate the left ventricular internal diameter in diastole, normalized for body weight (LVIDdN), the following formula was used:

$$LVIDdN = \frac{LVIDd}{body\ weight^{b}}$$

LVIDd is the M-mode measurement in cm, the body weight is in kg, and b is an exponent calculated by Cornell et al. (2004). In this case for LVIDd, the exponent is 0.294. LVIDdN is the normalized or indexed M-mode measurement. Cornell et al. (2004) states the reference is between 1.27 and 1.85. [28] See figure 5 for an example.

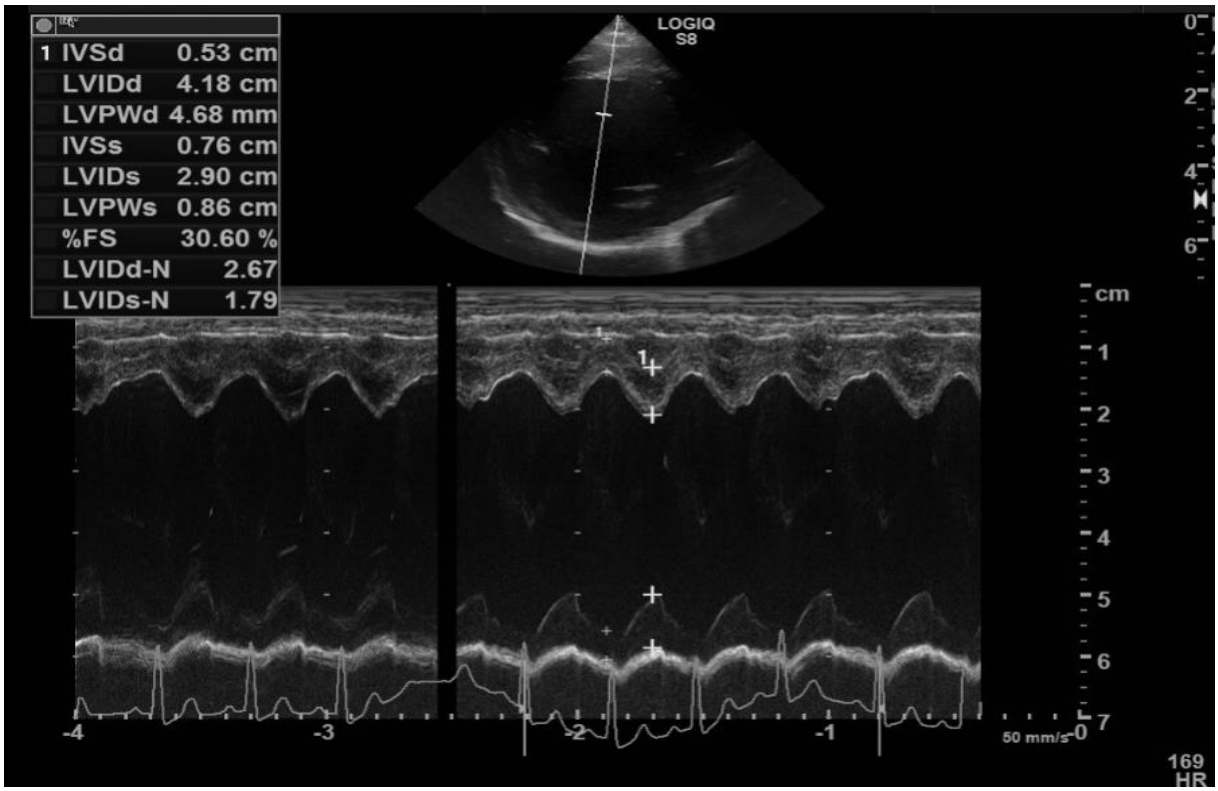

Figure 5 Measurement of the LIVDdN in a dog with PDA and left atrial enlargement. Used with permission of the Small Animal Cardiology Service, Department Clinical Sciences, Utrecht University.

Volume of the left ventricle
The volume of the left ventricle (LV) was measured with the use of Simpson's Method of Disc (SMOD) at end diastole. This measurement was executed on the left apical 4-chamber view and/or right parasternal long-axis 4-chamber view. The maximal LV length was assessed from the middle of a line connecting the hinge points of the mitral valve to the endocardial border of the LV apex. The LV area was assessed by tracing the endocardial border on each selected image. The ultrasound machine automatically calculated the LV volume. To obtain the end-diastolic volume index (EDVI), the LV volume was indexed to body surface area (BSA). The BSA was calculated with the formula 0.1 x $kg^{0.667}$. [29] The reference for EDVI in normal dogs used in this study is less than 70ml/m^2. [10] See figure 6 for an example.

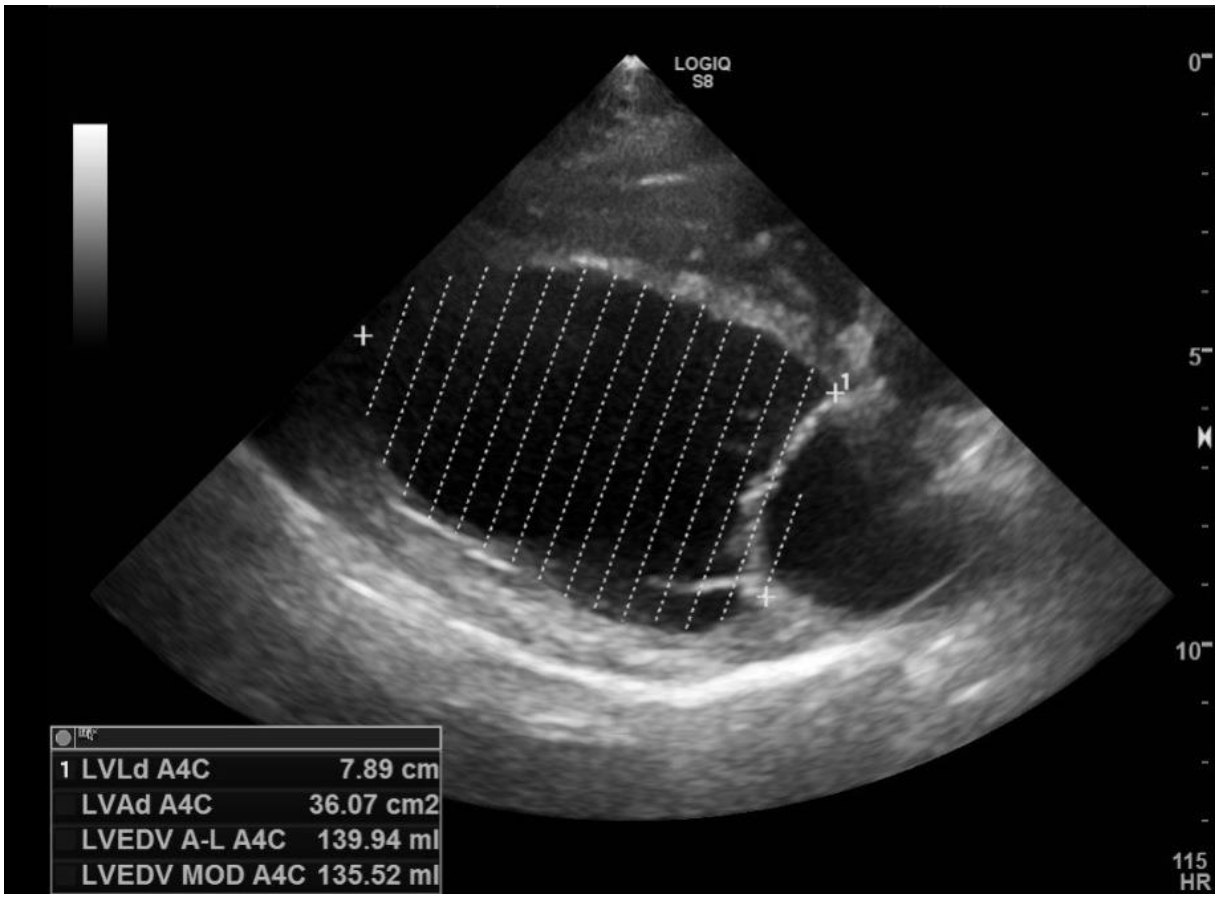

Figure 6 Measurement of the volume of the left ventricle, with the use of SMOD, in a dog with PDA and left atrial enlargement. Used with permission of the Small Animal Cardiology Service, Department Clinical Sciences, Utrecht University.

Pulmonary flow to systemic flow ratio

The pulmonary flow to systemic flow ratio (Qp:Qs) was assessed with 2-D echocardiography and pulsed-wave Doppler. The diameter of the Ao was measured at end-systole using the right parasternal 5-chamber view. The diameter of pulmonary artery (PA) was measured at end-systole using the transaortic short-axis view for PA. See figure 7A and B, respectively. The aortic and pulmonary flow velocity profiles were registered by pulsed-wave Doppler using the left apical 5-chamber view for Ao and the transaortic short-axis view for PA, see figure 7C and D, respectively. The sample volume (width of 2-4mm) was positioned within the arterial flow stream just distal to the opened pulmonic and aortic valves. Velocity time integrals were noted.

The systemic flow (Qs) was calculated with the following formula:

$$Systemic\ flow\ (mL) = \left(\pi\left(\frac{Ao}{2}\right)^2\right) x\ VTI_{Sys}$$

Ao is the aortic diameter (cm) and VTI_{Sys} is the mean of three consecutive velocity time integrals obtained from pulsed-wave Doppler traces of systolic aortic flow velocity (cm).

Pulmonary flow (Qp) was calculated with the following formula:

$$Pulmonary\ flow\ (mL) = \left(\pi\left(\frac{PA}{2}\right)^2\right) x\ VTI_{Pul}$$

PA is the pulmonary artery diameter (cm) and VTI_{Pul} is the mean of three consecutive velocity time integrals obtained from pulsed-wave Doppler traces of systolic pulmonary flow velocity (cm). [12] In the PDA the increased flow is seen in the ascending aorta, while the normal stroke volume is in the pulmonary artery. Calculation of the Qp:Qs is therefore the following [10]:

$$Qp{:}\,Qs = \frac{Systemic\ flow}{Pulmonary\ flow}$$

There are limitations to this technique. The main limiting factor is area calculation for the aorta and pulmonary artery. [10] The reference for the Qp:Qs in normal dogs used in this study is less than 1.00. [12]

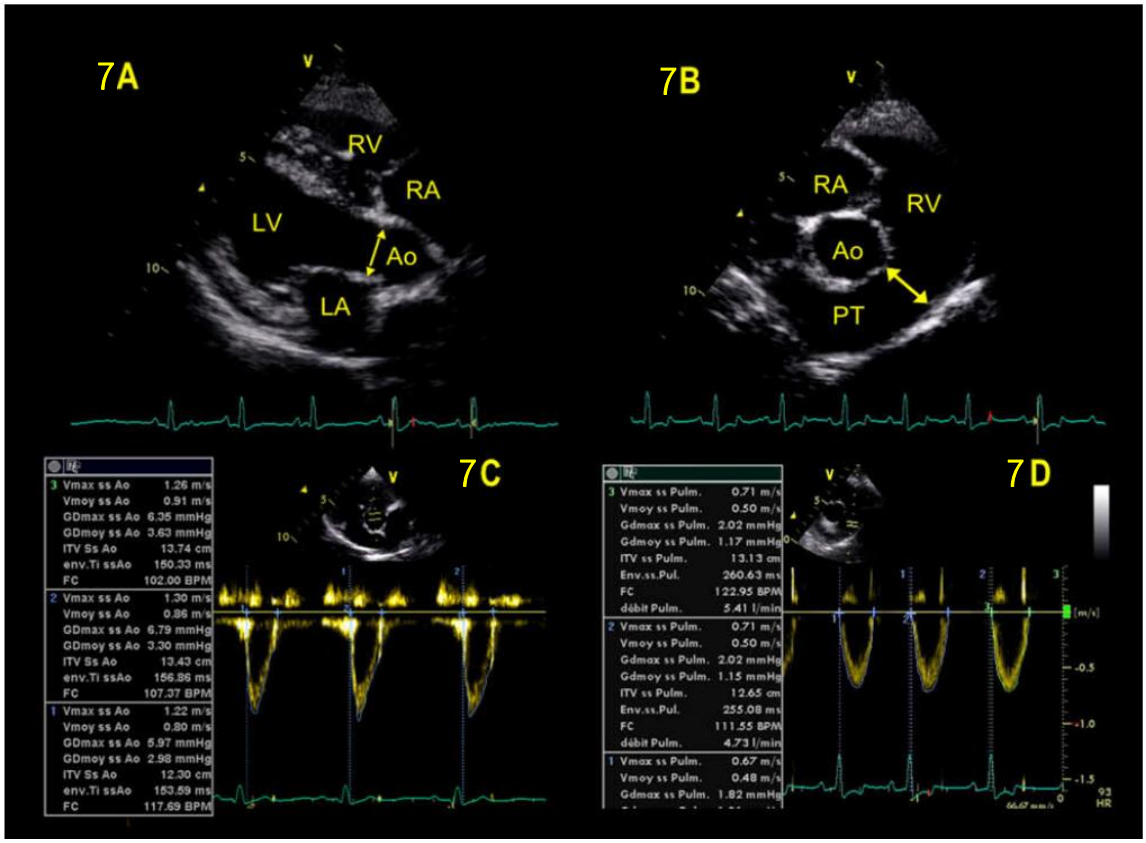

Figure 7 Measurement of Qp:Qs using 2-D echocardiography and pulsed-wave Doppler mode. 1A: Measurement of the systolic diameter of the aorta (Ao) at the height of the opened aortic valve using the right parasternal 5-chamber view. 1B: Measurement of the diameter of the systolic pulmonary artery (PA) at the height of the opened pulmonary valve using the right parasternal transaortic short-axis view. 1C: Measurement of the systolic aortic flow using pulsed-wave Doppler mode while in left apical 5-chamber view, with the Doppler sample located at the level of the opened aortic valve. 1D: Measurement of the systolic pulmonary flow using the pulsed-wave Doppler mode while in right parasternal transaortic short-axis view, with the Doppler sample located at the level of the opened pulmonary valve. From: Wess et al. (2010)

Abdominal aortic flow

Abdominal aortic flow was measured with the dogs in right lateral recumbency. The transducer was placed on the caudodorsal part of the abdomen, just ventral to the transverse processes of the lumbar vertebrae. The pulsating aorta was seen longitudinally just ventral to the vertebrae, to the left and parallel to the contiguous caudal vena cava. Pulsed-wave Doppler with a sample volume was used to measure the flow. During the examination of the aorta, the axis of the ultrasound beam and the axis of the vessel are parallel to each other, but their intersection angle should not exceed 60°. [30] To standardize the location of the measurement, the location of the view of the abdominal aorta was at the level of the second lumbar vertebrae, just caudal to the branching of the renal arteries. A more cranial position would have been difficult due to the ribs and gas-filled gastric fundus. According to Finn-Bodner et al. (1996), caudal to the renal arteries, the velocity in late diastole decreases and there is flow reversal in early diastole. This is because there is a high resistance of blood flow to the muscles of the hindquarter. [31]

The possible abnormal flow patterns of the descending aorta that are seen in infants with hsPDA, and that were investigated in the dogs of the study, are absent end diastolic flow and retrograde diastolic flow. [8] In healthy infants, the wave of the Doppler during diastole is anterograde, appearing in the same direction as the systole (figure 3B). This flow pattern is considered normal. When the wave in end diastole is not visible, the flow is absent (figure 3C). If the flow appears in the opposite direction than during the systole, it is retrograde (figure 3D). These two flow patterns are considered abnormal.

Measurements in control dogs
Dogs in the control group received a complete echocardiographic examination to confirm that they were either cardiovascularly healthy, suffering from a cardiac disease other than PDA, or having had their PDA fully closed through catheterization. Furthermore, the abdominal aortic flow was assessed.

Statistical analysis
This is a descriptive study. Microsoft Excel was used for basic descriptive statistical analyses. The data were expressed as mean ± standard deviation (SD).

Results

Patient Data
As stated in the Materials and Methods section, twenty dogs were included in this study: ten dogs in the research group and ten dogs in the control group. Among the ten dogs with PDA, five different breeds of dogs were represented in this study. The most frequent breeds were mongrel (N = 3) or Pomeranian (N = 2). All the dogs were female. The ages of the dogs ranged from 2,7 to 94 months (median, 6 months). The bodyweight ranged from 1,8 to 50,4 kg (median, 7,6kg).
Ten dogs were included in the control group. One was a healthy dog, two had a ventricular septal defect, two had pulmonic stenosis, one had mitral valve dysplasia and one a double-chambered right ventricle. Furthermore, three dogs with PDA were investigated after transcatheter closure.
Eight different breeds were represented in this group. Five dogs were female, and five dogs were male. The ages of the dogs ranged from 1,4 to 25,8 months (median, 4,6 months). The bodyweight ranged from 1,8 to 26,8 kg (median, 10,7 kg).

Echocardiographic Data
All dogs of the PDA group were confirmed with a left-to-right shunting PDA, using Color Doppler and 2-D echocardiography. They all had a peak velocity of the PDA of > 4 m/s (5,07 m/s ± 0,53).
Eight of the ten dogs had at least one of the investigated conventional echocardiographic parameters that was abnormal, thus their PDA was considered hemodynamically significant.
In three of the ten in the PDA group the LA:Ao was enlarged (1,46 ± 0,18). In eight of ten the LVIDdN was above the accepted range of normality, indicating enlargement (1,93 ± 0,26). In six of the ten the volume of the left ventricle was enlarged (80,38 ml/m^2 ± 25,67). The Qp:Qs was not calculated for two dogs, because the images were deemed to be of insufficient quality to provide a reliable measurement. Six of the eight remaining measurements were higher than the reference value. See Table 1 for details.

	PDA Ampulla (mm)	*PDA Ostium width (mm)*	*PDA velocity (m/s)*	*LA:Ao*	*LVIDdN*	*Left ventricle volume (ml/m²)*	*Qp:Qs*
Dog 1	7,0	2,1	5,93	1,71	2,11	114,41	0,90
Dog 2	5,4	1,4	5,33	1,61	1,93	60,67	1,19
Dog 3	5,0	1,9	5,56	1,4	1,89	85,06	1,16
Dog 4	9,6	2,4	5,73	1,37	1,86	103,76	1,11
Dog 5	4,8	1,0	5,11	1,20	1,52	44,31	0,94
Dog 6	7,1	2,6	4,56	1,59	2,07	92,63	-
Dog 7	7,1	2,8	4,67	1,48	2,03	100,39	1,06
Dog 8	8,4	2,3	4,54	1,66	2,19	54,22	-
Dog 9	7,5	2,4	5,43	1,40	2,27	99,15	1,87
Dog 10	6,1	2,6	4,9	1,19	1,47	49,23	1,45

Table 1 Echocardiographic data in dogs with PDA, including the PDA ampulla width, PDA ostium width, PDA velocity, left atrium to aorta ratio (LA:Ao, reference <1.6 [27]), internal diameter of the left ventricle (LVIDdN, reference >1.27 and <1.85[28]), volume of the left ventricle (reference <70ml/m² [10]) and the Qp:Qs (reference <1 [12]).

Visualization of the flow in the abdominal aorta

Visualization of the abdominal aorta was possible in all patients. Alignment with the aorta to have an insonation angle of less than 60° was possible in all cases. See figure 8 A to J.

Of the two dogs with no evidence of cardiac enlargement on echocardiography, one had normal abdominal aortic flow (dog 10, figure 8A), while the other had absent end-diastolic flow (dog 5, figure 8B).

Of the eight dogs with hsPDA, five dogs had retrograde flow (dog 6 to 9 and 3, respectively, figure 8C to 8F and 8G), one dog had a normal flow pattern (dog 1, figure 8H) and one dog had an alternating pattern between retrograde flow, absent end-diastolic flow, and normal flow. Because this dog was one of the dogs who was also investigated after cardiac catheterization, the post-ductal closure image was available and it was concluded that previous to closure, the flow was abnormal (dog 2, figure 8I). In one dog, the settings of the ultrasound were set incorrectly, which deemed the image to be of insufficient quality for assessment (dog 4, figure 8J). See figure 8 for further details.

What concerns the control group, all dogs had a normal flow in the abdominal aorta. See figure 9 for examples.

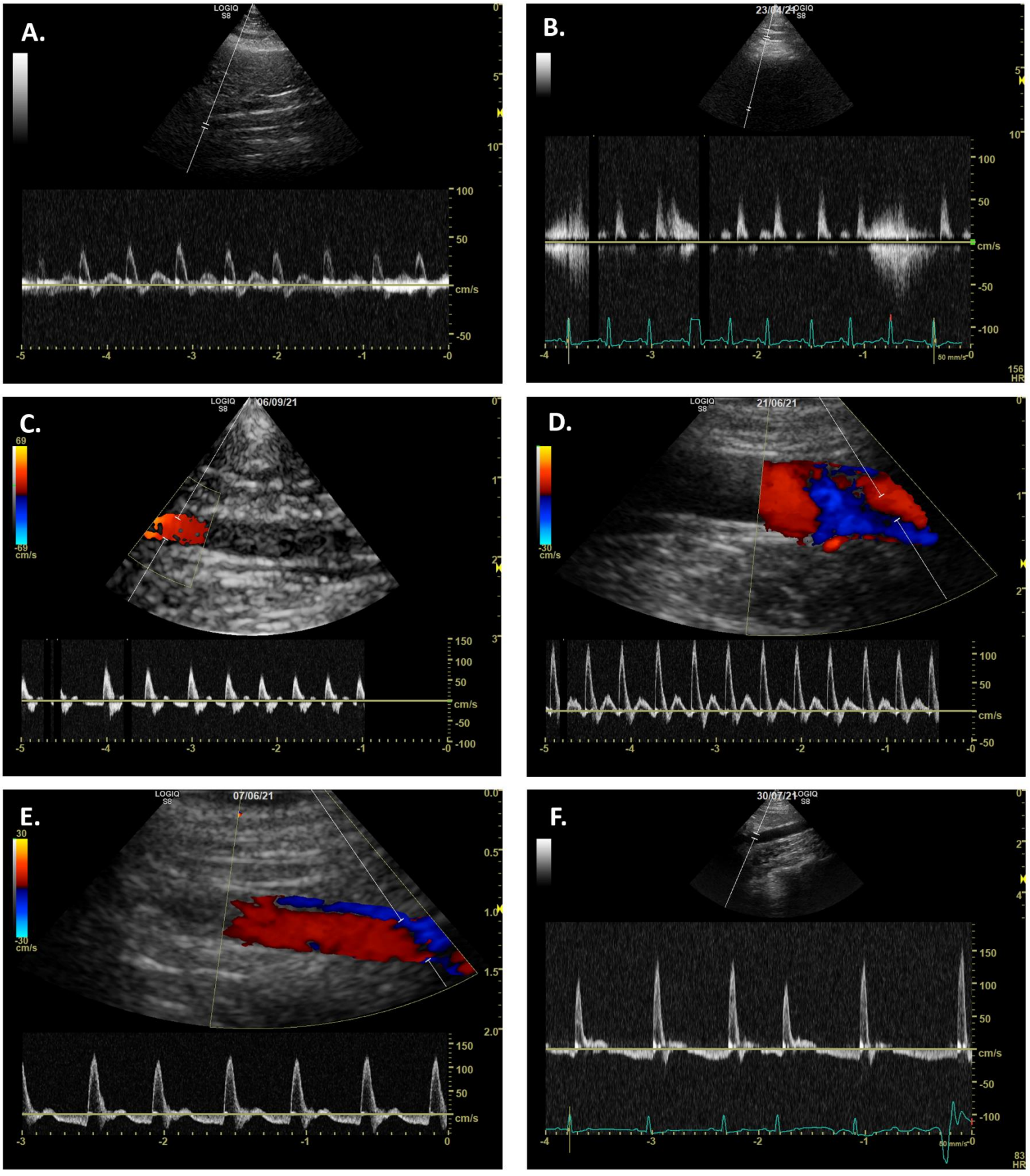

Figure 8 Abdominal aortic flow measured with pulsed-wave Doppler ultrasonography in dogs with PDA; A. Dog 10 with no cardiac enlargement on echocardiography and a normal flow pattern. B. Dog 5 with no cardiac enlargement on echocardiography and an absent flow pattern. C. to F. Dogs 6 to 9, respectively, with hsPDA with retrograde flow.

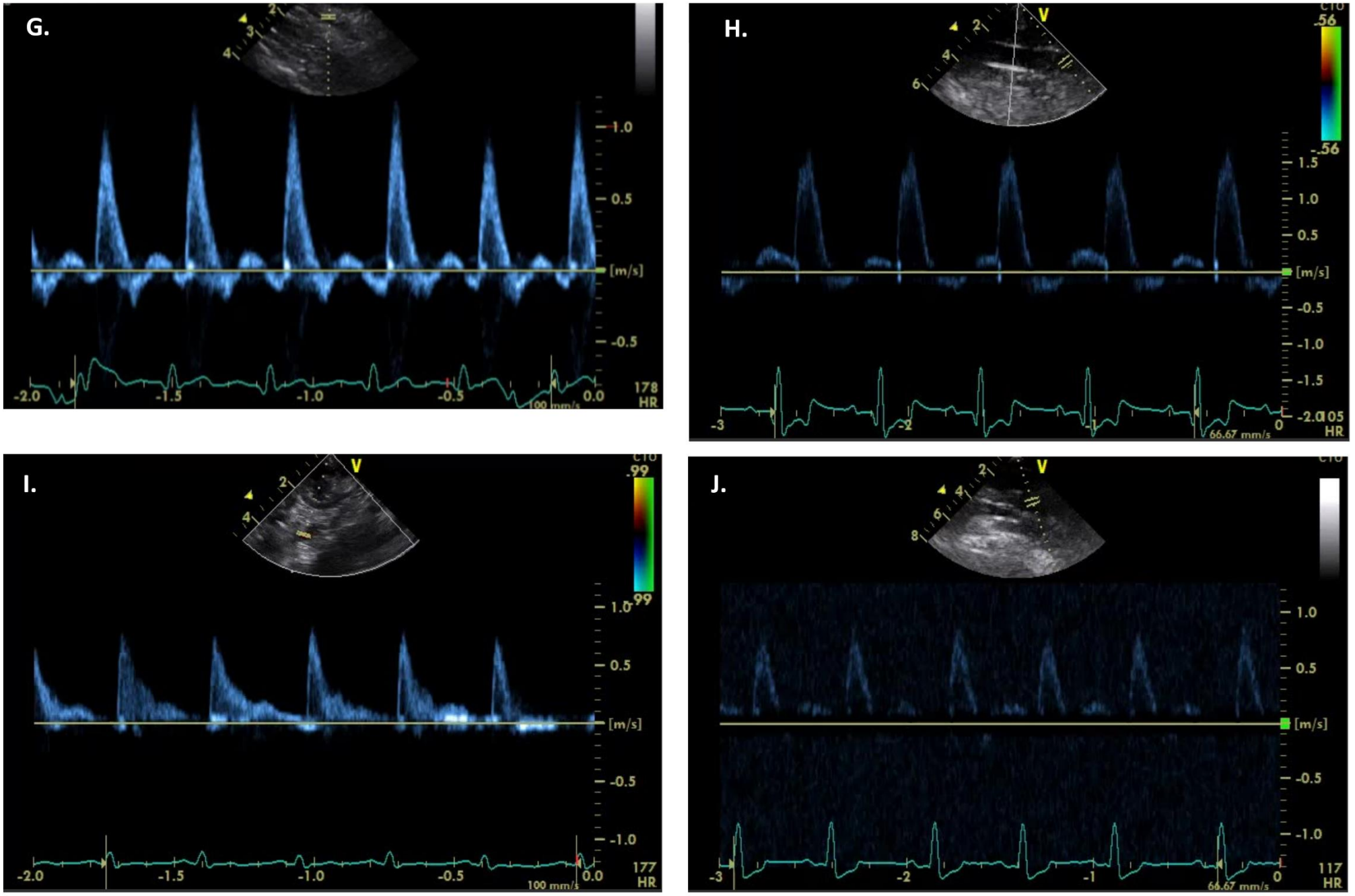

Figure 8 continued. Abdominal aortic flow measured with pulsed-wave Doppler ultrasonography in dogs with PDA; G. Dog 3 with hsPDA with retrograde flow pattern. H. Dog 1 with hsPDA with normal flow pattern. I. Dog 2 with hsPDA with alternating flow pattern. J. Dog 4 with hsPDA with image of insufficient quality for assessment.

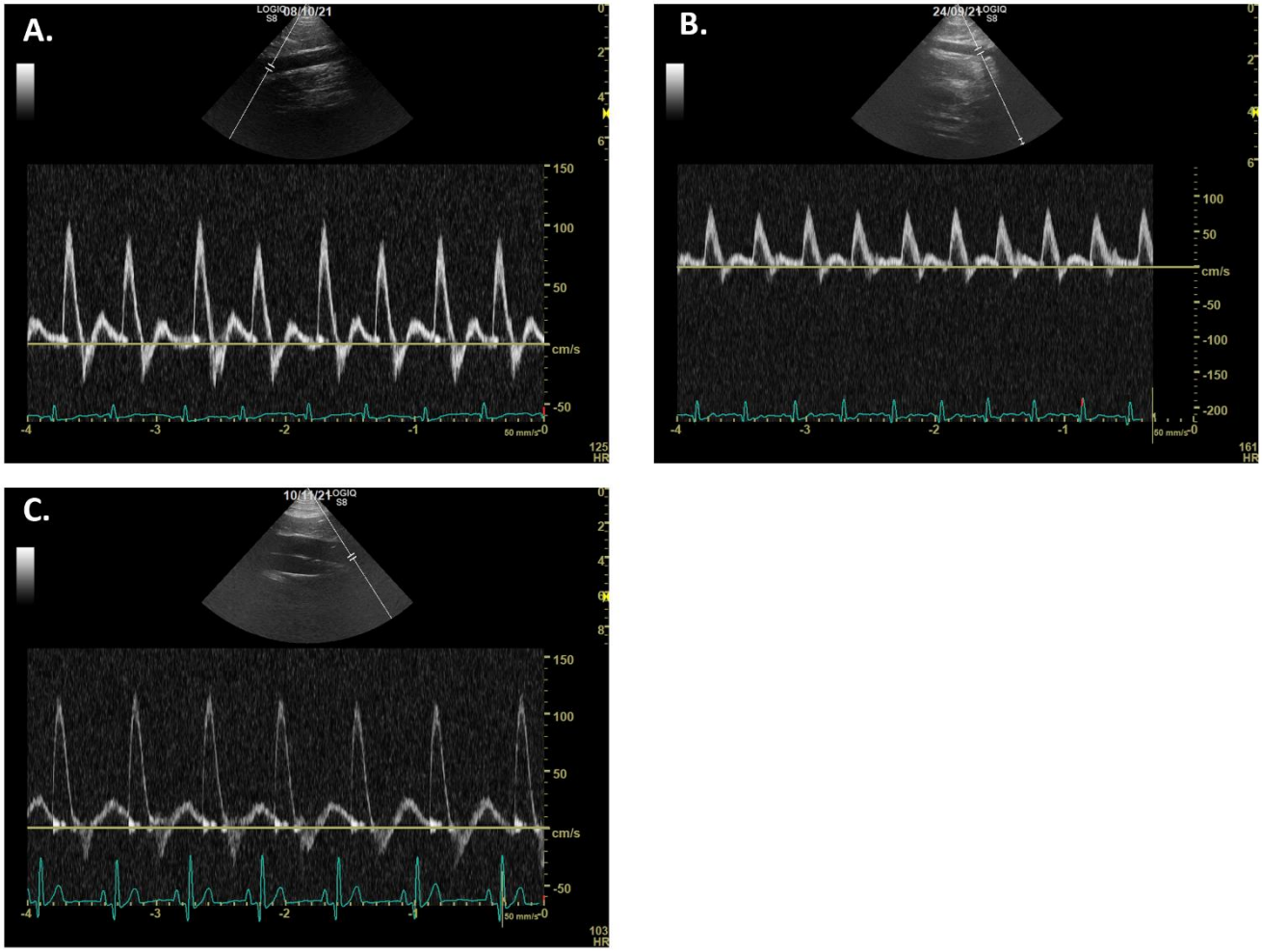

Figure 9 Normal abdominal aortic flow measured with pulsed-wave Doppler ultrasonography in dogs in the control group; A to C stands for dog 13, dog 14 and dog 11 of the control group, respectively

Discussion

The primary objective of this study, was to assess if the abnormalities of the flow in the descending aorta related to PDA as seen in humans with ultrasound, can be observed in the abdominal aorta of dogs with a hemodynamically significant PDA. Prior to that, it needed to be determined if assessment of the flow in the abdominal aorta with ultrasound in dogs was feasible. To our knowledge, this study is the first to research the flow in the abdominal aorta in dogs with PDA.

In humans, the visualization of the descending aorta is just distal to the PDA. [8] In dogs this is not an option due to the poor visibility and quality images of the thoracic descending aorta. [23] For that reason, it was decided to measure the aortic flow in the abdominal aorta. Fortunately, it was possible in all cases to visualize the flow in the abdominal aorta with ultrasound.

There are no clear guidelines within veterinary medicine to decide if a PDA is hemodynamically significant, but is widely accepted that this is the case if the heart is enlarged on echocardiography. Therefore, when the left heart showed any sign of enlargement, we considered the PDA to be hemodynamically significant. More specifically, we considered the heart to be enlarged, if at least one of the parameters (LA:Ao, volume of the left ventricle, or the LIVDdN [26–29]) was abnormal. A possible heart enlargement of the dogs in the control group was measured, but was deemed to be irrelevant for this study and not taken into account. This was because the measurements of the heart

were done to assess if the PDA in dogs is hemodynamically significant and the dogs in the control group do not have a PDA . The main objective of this study is the flow of the abdominal aorta. One of the measured parameters was the Qp:Qs ratio. Performing this measurement adequately is difficult in dogs with PDA. Since the flow of the PDA towards the pulmonary valves is so strong, the right ventricular outflow can be very difficult to visualize. For this reason, the Qp:Qs ratio was unfortunately not always deemed reliable, but this is known from literature. [12] Due to this fact, we decided not to use this parameter to assess the hemodynamic significance of the PDA.

The assessment of abdominal aortic flow was possible in all cases, but in one dog, interpretation of the diastolic flow was limited by a wrongly used filter during the ultrasound. This filter was used in only this patient, which was different than in the other patients. With this filter, the low velocities are not displayed, and since the diastolic flow can have very low velocity, it might be missed, making interpretation challenging and could create a false negative.

This study demonstrated that multiple dogs with hsPDA have an abnormal pattern of the flow in the abdominal aorta, compared to the control group in which there were none. The finding that dogs with hsPDA have an abnormal flow pattern, are consistent with various studies in humans. [8,13,14]

All dogs in the PDA group were female. This was expected based on multiple studies, since the prevalence of PDA in female dogs is two or more times higher than in male dogs. [4,5]

In the control group, dogs with congenital heart disease other than PDA were included, besides dogs that were healthy and dogs that were their own control. It was presumed that these conditions did not interfere with the data of the flow in the abdominal aorta, because when shunting was present such as in dogs with ventricular septal defect, this was in the heart and not external to the heart, therefore the abdominal aortic diastolic flow was not expected to be altered. In fact, when the aortic valves are closed and in absence of aortic insufficiency, there should be no difference of flow between a healthy dog and dogs with the congenital heart diseases other than PDA included.

One dog had no heart enlargement and was considered not to have hsPDA, but the abdominal aortic flow was absent during end-diastole. A possible explanation for this phenomenon is that the ultrasound is done in the early stages of the disease, hence no compensation of the heart, yet, while the flow in the abdominal aorta might already show the hemodynamic relevance of the PDA. It might also be a false positive measurement due to technical factors, such as exaggerated filtering of low velocities leading to artefact. Another dog with a hsPDA had an alternating flow pattern, which was considered abnormal. The alternating flow pattern might be due to movement of the patient or of the probe.

The heart rate of the patient might also have an effect on the assessment of the flow in the abdominal aorta. With a higher heart rate, the diastole is shorter and therefore less time for the flow to stop or reverse. The heart rate in adult humans is between 60-100bpm, [32] in dogs in rest it is between 60-120bpm, [33] but in reality on the examination table it is higher, up to 180bpm. But since PDA in humans is mainly a disorder seen in preterm infants, the heart rate is comparable between the two species, because the heart rate in preterm infants is between 90-200bpm, depending on gestational age. [34] In the studies on the hsPDA in humans [8,13,14], it is not mentioned to be a limiting factor for the assessment of the flow in the descending aorta. The heart rate cannot be standardized between the patients.

For treatment of the PDA in dogs, the assessment of the abdominal aortic flow alone will probably not change the management of the patient. But in combination with all the other parameters, it could be useful to make a weighted decision. When the parameters are all normal and there is a normal flow in the abdominal aorta, closure of the PDA might not be necessary. For example, in this

study, patient 10 is a 3,5-year-old dog with a small PDA, with a normal flow in the abdominal aorta and no signs of heart enlargement. The PDA in this dog has not been closed as yet. The other way around, when all the parameters are normal, but the flow in the abdominal aorta is abnormal, closure might be recommendable. So, the flow in the abdominal aorta might become another parameter to assess when deciding if closure of the PDA is needed.

This study has some limitations. The investigators in this study were not blinded, which can imply observer bias. In a potential follow-up study, this can be prevented by showing the images to an investigator, who was not there at the moment of examination, and has no information regarding the patients. Blind assessment of the abdominal aortic flow can therefore be performed. Furthermore, in the protocol of a potential follow-up study, attainment of good quality images must be an inclusion criterion and filtering of the velocities obtained by ultrasound must be standardized. In this study, one image was deemed of insufficient quality to assess the flow in the abdominal aorta. That is why it should be included in the protocol to avoid the filtering of low velocities and prevent differences between the subjects.

Standardizing the control group would also be a way to improve this study. There are two options to standardize. Firstly, the control group could consist of all healthy dogs, to prevent any possible effect of other heart disease on the flow in the abdominal aorta, even though in this study it was presumed not to have any effect. Secondly, the control group could consist of all dogs with PDA, which are measured again after closure of the PDA. That way the population is standardized immediately for weight, age and so on, and the effect of closing the PDA on the flow in the abdominal aorta can be added to the research. Presence of residual flow after closure should in this case be excluded or acknowledged.

Further research is necessary with inclusion of a bigger population to improve assessment of the significance of the effect of a hsPDA on the flow in the abdominal aorta compared to a control group. Another possible research could be the follow up after the owner decided not to close the hsPDA and investigate how the flow changes over time as the diseases progresses and even discuss the possibility of linking a life expectancy to it, from the point the flow becomes abnormal.
An additional possible follow-up research can be done to come to gather more information, for example define if older dogs with unclosed PDA's have a normal flow in the abdominal aorta.

The small sample sizes should be a reason for caution when interpreting the results, but the following (preliminary) conclusions can be drawn: firstly, the use of ultrasound to assess the flow in the abdominal aorta is feasible, providing low velocities are filtered adequately. Secondly, the presence of absent or retrograde flow in the descending aorta in humans with hsPDA, is also seen in dogs with hsPDA in the abdominal aorta, and not in the control group in dogs without PDA. So, the detection of absent or retrograde diastolic flow seems a strong indicator of hsPDA. Further research is necessary and confirming the diagnostic power of such a non-invasive, animal-friendly approach, seems of substantial value.

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