Infective endocarditis of the aortic valve in a Border collie dog with patent ductus arteriosus

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ABSTRACT.   Infective endocarditis (IE) in dogs with cardiac shunts has not been reported previously. However, we encountered a dog with concurrent patent ductus arteriosus (PDA) and IE. The dog was a 1-year-old, 13.9-kg female Border collie and presented with anorexia, weight loss, pyrexia (40.4°C) and lameness. A continuous murmur with maximal intensity over the left heart base (Levine 5/6) was detected on auscultation. Echocardiography revealed a PDA and severe aortic stenosis (AS) caused by aortic-valve vegetative lesions. *Corynebacterium* spp. and *Bacillus subtilis* were isolated from blood cultures. The dog responded to aggressive antibiotic therapy, and the PDA was subsequently surgically corrected. After a series of treatments, the dog showed long-term improvement in clinical status.
KEY WORDS: canine, infective endocarditis, patent ductus arteriosus

Infective endocarditis (IE) is a rare cardiac disease in which bacterial or fungal infections cause inflammation of the endocardium. Patients with structural heart disease are predisposed to IE, and it has been reported that dogs with congenital heart disease involving subaortic stenosis are also predisposed to the disease [17]. In humans, both patent ductus arteriosus (PDA) and ventricular septal defect are underlying factors promoting IE [29]. In PDA patients, infection usually occurs on the endothelium of the ductus arteriosus, pulmonary trunk and left pulmonary artery, which are exposed to the abnormal blood jet flow caused by the shunt [9, 29]. However, IE involving not only the ductus arteriosus and pulmonary artery, but also the aortic valve is extremely rare, even in humans [9]. In dogs, there is no known case of IE associated with PDA, although device infection has been reported following transcutaneous occlusion of PDA in dogs [14, 38]. Therefore, our case of concurrent PDA and IE is noteworthy, although no definite relationship between the 2 conditions was elucidated. Although aortic-valve infection due to IE is associated with a poor prognosis in dogs [21], this particular patient's clinical status improved after aggressive antibiotic therapy and surgical PDA correction. This novel case is presented below.

A 1-year-old intact female Border collie dog, weighing 13.9 kg, was presented to the referring veterinarian due to a 1-month history of anorexia and vomiting, weight loss (16.9%/month) and lameness in the right hind limb. Pyrexia on physical examination raised the suspicion of infection. Empiric antibiotic therapy was initiated, and the clinical status of the dog improved. However, the dog was then referred to our veterinary hospital at Azabu University due to continued pyrexia and an existing cardiac murmur that was detected during puppyhood.

On physical examination, the patient's body temperature was 38.5°C, and heart rate was 112 bpm; however, respiration was rapid (80/min) and labored. Auscultation revealed a continuous murmur with maximal intensity over the left heart base (Levine 5/6). In addition, bounding pulses were detected in the femoral arteries and the distal arteries of all 4 limbs, i.e., the median arteries in the forelimbs and the saphenous arteries in the hind limbs. Thoracic radiography revealed cardiomegaly; the vertebral heart score was 11.6 vertebrae [v] (reference range, 9.7 ± 0.5 v [6]), the pulmonary vessels were enlarged, and the right caudal lung lobe showed increased opacity. Pulmonary edema was suspected, and the patient was administered furosemide (1 mg/kg, intravenously [IV]) and pimobendan (0.36 mg/kg, per os [PO]) and placed in an oxygen cage providing a 40% inspiratory oxygen fraction. After 2 hr, the respiration was no longer labored, and the respiratory rate decreased to 52 breaths/min. Electrocardiography revealed a prolonged QRS duration, i.e., 80 msec, but no arrhythmia was detected during the 5-min examination.

Echocardiography showed left ventricular enlargement, indicated by a normalized left ventricular end-diastolic diameter (LVDd-index) of 2.91 (reference range, 1.27–1.85 [11]). Contractile dysfunction, indicated by a normalized left

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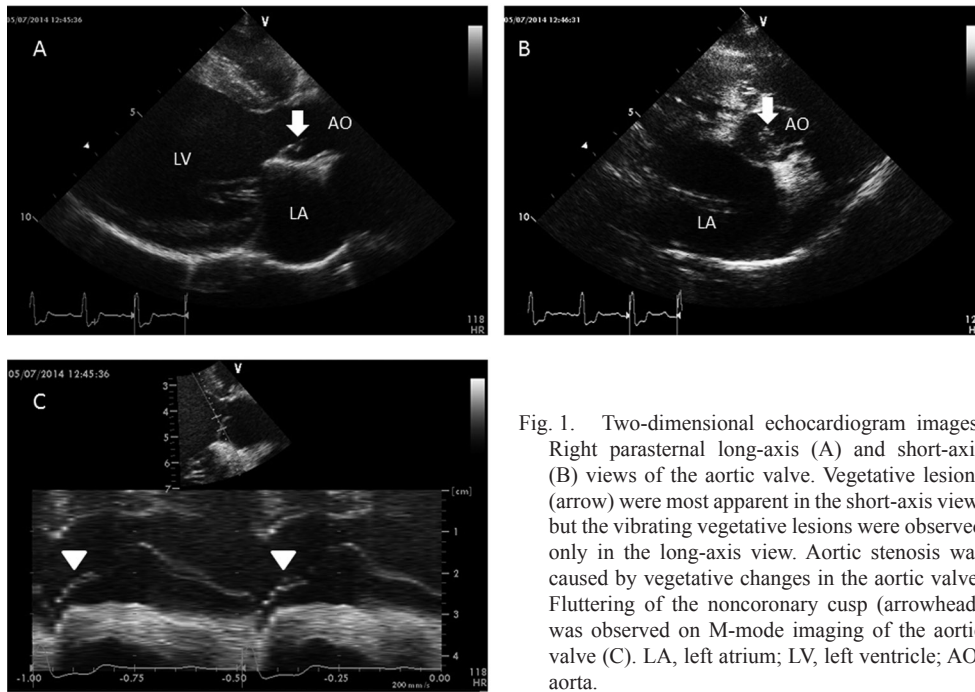
Fig. 1. Two-dimensional echocardiogram images. Right parasternal long-axis (A) and short-axis (B) views of the aortic valve. Vegetative lesions (arrow) were most apparent in the short-axis view, but the vibrating vegetative lesions were observed only in the long-axis view. Aortic stenosis was caused by vegetative changes in the aortic valve. Fluttering of the noncoronary cusp (arrowhead) was observed on M-mode imaging of the aortic valve (C). LA, left atrium; LV, left ventricle; AO, aorta.

ventricular end-systolic diameter (LVDs-index) of 2.13 (reference range, 0.71–1.26 [11]) and fractional shortening (FS) of 22.63% (reference range, >25% [11]), was also observed. Color flow Doppler showed a left-to-right PDA with a maximal flow velocity of 4.63 m/sec (reference range, >3.5 m/sec [25]), severe aortic valve stenosis (AS) with a peak velocity of 5.01 m/sec (reference range, <2 m/sec [16]) and severe aortic regurgitation (AR) extending to the left ventricular apex. Two-dimensional echocardiography revealed fluttering vegetative lesions on the aortic valve (Fig. 1). A complete blood count showed non-regenerative anemia, indicated by a red blood cell count of 418.0×10^4 cells/μl, packed cell volume of 27.7%, hemoglobin concentration of 9.5 g/dl and reticulocyte count of 4.3×10^4 cells/μl; an elevated white blood cell count (25,750 cells/μl) and neutrophilia (20,460 cells/μl). Biochemical analysis and coagulation tests including evaluation of fibrin degradation products did not show any significant abnormalities, although the C-reactive protein (CRP) concentration was elevated at 18.0 mg/dl (reference range, <1.0 mg/dl). Three blood culture samples were aseptically collected in resin-containing blood culturettes from both jugular veins and the left saphenous vein at 1-hr intervals. The three 5-ml samples of blood were each used for aerobic and anaerobic cultures (HOKENKAGAKUKENKYUUJYO Co., Ltd., Yokohama, Japan). *Corynebacterium* spp. were isolated from the left jugular vein and left saphenous vein, and *Bacillus subtilis* was isolated from the right jugular vein. No abnormalities were detected on urinalysis, and no pathogens were cultured from the urine. Joint fluid from the right stifle was examined cytologically due to joint swelling and revealed inflammation with mononuclear cells, although the bacterial culture yielded negative results. Radiography of the

right stifle showed periarticular swelling. Factors predisposing the patients to sustained bacteremia, e.g., diabetes mellitus, discitis, periodontal disease, pyoderma, abscess caused by bite or scratch wounds and immune-suppressing drugs, were not detected.

The dog was diagnosed with left-to-right PDA and with severe AS and AR due to aortic valve IE. The dog was hospitalized due to congestive heart failure, and aggressive antibiotic and heart failure therapy was initiated. Pimobendan (0.36 mg/kg, PO, q 12 hr), enalapril maleate (0.36 mg/kg, PO, q 12 hr) and furosemide (1 mg/kg, IV, q 12 hr) were administered to treat the heart failure. Cefazolin (22 mg/kg, IV, q 8 hr) and enrofloxacin (5 mg/kg, subcutaneously [SC], q 24 hr), which were initially prescribed empirically at the first presentation, were continued, because both *Corynebacterium* spp. and *Bacillus subtilis* were sensitive to cefazolin and quinolones according to the results of antibiotic susceptibility testing. The pathogens were also sensitive to ampicillin, penicillin, cefotaxime, cefdinir, cefepime, imipenem, erythromycin, minocycline, amikacin, vancomycin and gentamycin. Famotidine (0.5 mg/kg, IV, q 12 hr) was used to treat vomiting, and heparin (100 IU/kg, SC, q 12 hr) was used to prevent disseminated intravascular clotting. Intravenous catheters were replaced every 5 to 7 days according to the status of the catheter insertion site.

At 2 days after presentation at our institution, the patient showed significant clinical improvement; her activity and appetite completely recovered at 3 days. At 10 days, the furosemide was switched from parenteral to oral administration and the dose reduced (1.1 mg/kg, PO, q 24 hr), because her clinical status was excellent. At 16 days, the patient's body temperature was 38.2°C, and the anemia and neutrophilia

had resolved. Blood culture of samples from the jugular vein and left saphenous vein was repeated and yielded negative results. Famotidine was discontinued, because the anorexia and vomiting had resolved. Echocardiography showed that the peak velocity of the AS was 4.88 m/sec. The peak velocity and pressure half time (PHT) of the AR were 2.85 m/sec and 111.8 msec, respectively. The low diastolic pressure due to PDA and AR was suspected because of the low gradient pressure between the aorta and the left ventricle in diastole, although the beam/flow angle was inadequate. At 20 days, heparin was discontinued, because the CRP concentration had significantly decreased (2.25 mg/d*l*).

At 21 days, the patient underwent surgical ligation of the ductus arteriosus. General anesthesia was induced with fentanyl (10 μg/kg, IV), midazolam (0.2 mg/kg, IV) and propofol (1–2 mg/kg, IV) and maintained with fentanyl (5 μg/kg/hr, constant-rate infusion [CRI]) and isoflurane (1.5–2.0% in 100% oxygen). Thoracotomy was performed via the left fourth intercostal space. For ductus arteriosus ligation, the standard dissection technique was selected instead of the Jackson and Henderson dissection (JH) method, because the ductus arteriosus was enlarged as a result of tubular aneurysm formation, and the heart size was too large to allow isolation of the dorsal descending aorta. In addition, the descending aorta was beating strongly due to the significant bounding pulse. The ductus arteriosus was closed with 1–0 silk and surgical silk tape (Fig. 2). The remaining thoracic musculature, subcutaneous tissue and skin were closed routinely, and the dog recovered uneventfully from general anesthesia. Fentanyl (2 μg/kg/hr, CRI) provided analgesia for 24 hr postoperatively. The dog remained in an oxygen cage (40% inspired oxygen) for 2 days postoperatively due to a low percutaneous oxygen saturation measurement of 94%. The heart failure therapy and parenteral antibiotic therapy were continued postoperatively. Echocardiography was repeated immediately postoperatively and showed the disappearance of the PDA; however, the AS and AR remained and showed peak velocities of 3.96 m/sec and 6.25 m/sec, respectively. The PHT of the AR was 100.0 msec.

At 33 days after presentation at our institution, echocardiography was repeated to elucidate the cause of the persistent bounding pulses and the to-and-fro murmur on auscultation, which had a maximal intensity over the left heart base (Levine 3/6). Echocardiography revealed a slight residual shunt through the ductus arteriosus; furthermore, the echocardiographic parameters had worsened from their preoperative values. The LA/Ao pre- and postoperatively were 1.45 and 1.78, respectively; the pre- and postoperative LVDd-index and LVDs-index values were respectively 2.91 and 3.23 and 2.13 and 2.29. However, the aortic flow velocity had decreased to 3.66 m/sec. The vegetative lesions on the aortic valve cusps had disappeared on 2-dimensional echocardiography; however, the cusps were deformed and highly echogenic. At 34 days after presentation, the blood pressure was measured as 153 mmHg using the Doppler method. Parenteral antibiotic therapy was discontinued, because the dog was bright and had no clinical symptoms associated with infection, and she was discharged. Amoxicillin-clavulanic
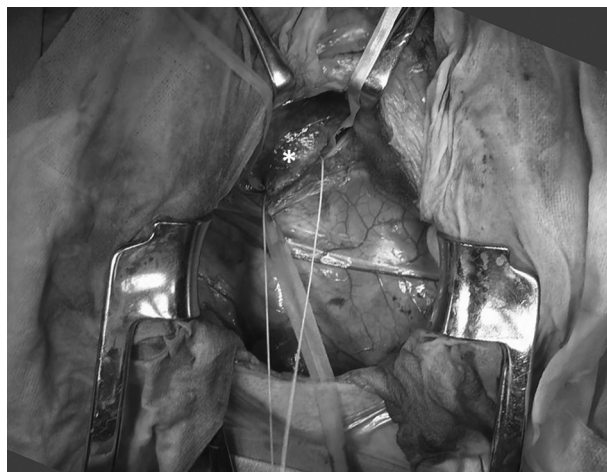

Fig. 2. Surgeon's view of patent ductus arteriosus (PDA) ligation. The PDA was large, because of tubular aneurism (asterisk) formation. In addition, the vessels were strongly beating, because of the bounding pulse due to the PDA and aortic regurgitation.

acid (18 mg/kg, PO, q 12 hr) was administered for 10 days after discharge from hospital. Pimobendan (0.36 mg/kg, PO, q 12 hr), enalapril maleate (0.36 mg/kg, PO, q 12 hr) and furosemide (1.1 mg/kg, PO, as needed according to respiratory rate) were used to manage the heart failure.

At 44 days after presentation at our institution, the dog returned due to swelling of the dorsal cervical skin. However, the site of the swelling appeared to match the position where enrofloxacin had been repeatedly administered. The dog was also coughing 3 to 4 times daily, although her clinical status was excellent. Thoracic radiography revealed cardiomegaly (VHS=11.9 v) and enlarged pulmonary veins without pulmonary edema. On echocardiography, the left ventricular diameter was decreased (LVDd-index=3.11) compared to the value at 33 days, and the left ventricular contractility had improved (LVDs-index=1.96 and FS=33.5%) compared to the values at first presentation and at 33 days. However, the aortic flow velocity had increased to 4.51 m/sec, perhaps because the contractility of the left ventricle improved. Typically, a severe AS is treated with atenolol due to its negative inotropic and anti-arrhythmic effects, but the AS was not treated in this case because the left ventricular contractility was insufficient. AR extended to the left ventricular apex and was observed at the same level as that before surgery. The AR peak velocity was 4.6 m/sec and the PHT 159.4 msec. There was a risk of further worsening of the AS with use of an afterload reducer, but we elected to administer amlodipine at a low dosage (0.1 mg/kg q 24 hr) and increase it gradually to 0.2 mg/kg q 12 hr while monitoring the blood pressure because the benefit of decreasing the AR was deemed to outweigh the risk of AS deterioration.

At 91 days after presentation, the LVDd-index and LVDs-index decreased to 2.97 and 1.85, respectively, compared to those at 44 days after presentation. In addition, the LA/Ao decreased from its postoperative value of 1.78 to 1.27.

However, the AS peak velocity increased further to 4.39 m/sec compared to that at 44 days after presentation. The AR peak velocity and PHT were 4.95 m/sec and 224.08 msec, respectively. The dog was in excellent clinical status, and the owner was satisfied with the outcome.

The prevalence of IE in dogs is low at 0.09–0.6%, but it may be underestimated, because dogs with IE display non-specific clinical signs, and diagnosis is difficult. IE lesions diagnosed postmortem may not be visible on echocardiography [14, 34]. IE is associated with damaged endocardium and/or endothelium and sustained bacteremia. Predisposing factors of IE in dogs are diabetes mellitus [27], discitis, pneumonia, infective arthritis, prostatitis, periodontal disease, urinary infection, pyoderma, abscess formation at bite or scratch wounds, congenital heart disease, central venous catheter placement and the use of immune-suppressing drugs [8, 20]. In this report, the dog had PDA, which is a predisposing factor in humans [10]. However, there are no cases of concurrent IE and PDA in previous reports describing PDA in 520 dogs [31], in 170 dogs with PDA that presented at our university from 1999 to 2009 (unpublished data) or in 71 dogs with IE [34]. In veterinary medicine, only dogs with subaortic stenosis appear to be at a high risk of IE [13]. The most common sites of infection are the ductus arteriosus, pulmonary artery trunk and left pulmonary artery, which, in humans with PDA, are exposed to abnormal jet flow due to the cardiac shunt; aortic-valve infection is extremely rare, even in humans with PDA [9]. IE may occur at the aortic valve in dogs with subaortic stenosis, because jet flow damages the endocardium of the aortic valve [26, 32, 34]. Reportedly, dogs with PDA may have high aortic velocity (up to 3.75 m/s) due to volume overload [2, 23]. This high aortic velocity following volume overload in PDA may damage the aortic valve endocardium. The dog in this report may have underlying aortic stenosis; however, the existence of congenital aortic stenosis cannot be confirmed by antemortem diagnosis, because the pathologic changes in the aortic valve following IE do not completely resolve with antibiotic therapy in all dogs with IE [34]. In addition, small vegetative lesions that could not be visualized by echocardiography may have existed on the endothelium of the ductus arteriosus and/or the pulmonary artery in this case. Indeed, IE lesions that were not detected by echocardiography were later diagnosed by necropsy in dogs [34]. Although the left ventricular side of the aortic valve should have IE in cases of turbulent flow at the left ventricular outflow, because the ventricular side of the aortic valve was exposed to the jet flow in this dog, the opposite side of aortic valve instead showed IE on echocardiography. The exact location of IE lesions is unclear without postmortem diagnosis [34], but a vegetative lesion originating from the left ventricular side of the aortic valve may extend distally due to blood flow.

Sustained bacteremia following infective arthritis or urinary infection is suspected in this case; however, bacterial cultures showed negative results for both joint fluid and urine samples, although they might have been false-negative results due to the antibiotic therapy. The lameness may have been due to deposition of immune complexes in response to the bacteremia [20] as the distal artery of the lame right hind limb was palpable, which is not observed in dogs with septic thromboembolism [34]. The presence of *Corynebacterium* spp. may reflect contamination in this dog, because it was isolated from only 2 of 3 blood cultures; however, in humans, it has been reported that 80% of bacteremic episodes were detected with the first culture, 88% with the first 2 cultures and 99% with 3 cultures when blood was sampled in sequence [36]. Therefore, it was unnecessary for all 3 samples to test positive, and *Corynebacterium* spp. may in fact have been the cause of IE in this dog. *Corynebacterium* spp. inhabit the skin and mucous membranes of humans and animals [35]. Therefore, periodontal disease, pyoderma and abscess formation at bite or scratch wounds may cause IE, although these events did not occur in the present report. *Bacillus subtilis* was also isolated from blood culture in this dog. *Bacillus subtilis* is a soil bacterium and is a common cause of pseudobacteremia following contamination [12, 39], but it is considered a rare cause of IE in humans [28]. Whether *Bacillus subtilis* was the cause of IE is unclear in this case, but regardless, it was sensitive to the antibiotics that were administered.

A lower respiratory infection may also have been the cause of sustained bacteremia, because the dog continued to cough after heart failure therapy was initiated. However, *Corynebacterium* spp. and *Bacillus subtilis* have not been reported as pathogenic organisms in lower respiratory infections [1]. The origin of the sustained bacteremia could not be identified in this dog, but it is reportedly difficult to confirm the origin of bacteremia in dogs with IE [18]. Immune deficiency is another potential trigger [18]; however, infection did not recur in this dog after she recovered from the IE. In dogs, *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, *Bartonella* spp. and *Corynebacterium* spp. are reported pathogens in IE [20, 21]. These organisms are not isolated by blood culture in 60–70% of dogs with IE [23, 27]. In this case, the pathogenic organism was isolated from the blood despite antibiotic use prior to blood culture, perhaps because resin-containing blood culturettes were used. The blood cultures were collected from the veins only in this dog, because a large volume could be easily withdrawn, but it is preferable to collect blood from the arteries, such as the aortic or mitral valve, especially in dogs with pathologic lesions following left-heart IE. However, in humans, arterial blood cultures were not associated with higher diagnostic yields than venous blood cultures [37]. There are no established antibiotic therapeutic protocols for IE, but intravenous antibiotic therapy for 1 to 2 weeks followed by oral administration for 6 to 8 weeks has been empirically performed in dogs [20]. The dog in this report received parenteral antibiotics for 33 days based on the antibiotic susceptibility test results, similar to the protocol in humans with IE. However, alternative methods employing oral or subcutaneous antibiotic administration [4] at home should be considered in cases with financial restrictions.

Ductus arteriosus closure was difficult to justify in this case, because dogs with aortic valve infection due to IE have a very poor prognosis; the median survival time is only 3 days [21]. However, the decision was made to proceed with

ductus arteriosus closure in this case, because (1) the clinical status significantly improved after aggressive antibiotic therapy, (2) humans with PDA reportedly have a high risk of IE [10], (3) only 36% of dogs with PDA survive to 1 year of age [13] and (4) untreated PDA has a poor prognosis in dogs [31]. In addition, the dog in this report had no negative survival factors previously reported in dogs with IE, such as thrombocytopenia, elevated serum creatinine concentration, renal dysfunction and thromboembolism [34]. The ductus arteriosus was surgically ligated rather than closed with a device, because ductus arteriosus-closure devices increase the risk of infection [14, 38]. However, a slight residual shunt through the ductus arteriosus was observed after surgery. It has been reported that a residual shunt occurs in 35.3% of dogs that undergo ductus arteriosus ligation, particularly with the JH method [33]. In the JH method, entrapment of loose connective tissue within the medial aspect of the ligature results in recanalization of the PDA [5, 33]. In this case, the shunt flow through the PDA initially disappeared immediately after ductus arteriosus closure, but the residual shunt was observed 12 days postoperatively. The recanalization of the PDA was caused by the entrapment of loose connective tissue within the medial aspect of the ligature due to the large size of the ductus arteriosus. However, this may reflect our technical limitation, because the standard dissection technique was utilized for PDA ligation in this case. Namely, the PDA may not have been completely ligated in this case, because the PDA had become a large tubular aneurysm with a bounding pulse in the ductus vessels due to the PDA and AR.

The risk of IE disappears after PDA closure in humans [10], and dogs with residual PDA shunts do not develop IE [13, 20, 33]. In addition, residual shunts occur in 14% of humans within 6 months after transcutaneous occlusion of PDA. IE associated with residual PDA shunts is extremely rare [30]; therefore, residual shunts appear not to require additional treatment in dogs unless there are negative hemodynamic effects, which may have been the case in this dog. The dog was doing well clinically, but the echocariographic parameters worsened postoperatively. Potentially, the dog in this report may have developed acute AS and AR following IE, which then decreased the left ventricular compliance. That the improved clinical status was inversely related to the echocardiographic parameters likely reflected the compensatory mechanisms of heart failure during treatment [20]. AS remained moderate to severe after initiating treatment for PDA; it may have improved postoperatively due to the siginificantly decreased volume overload following ductus arteriosus occlusion [2] or improvement of the aortic valve structure after beginning antibiotic treatment [18, 20]. Severe AS is treated with atenolol, surgical correction or baloon valvulopasty; however, in the present case, the AS was not treated due to insufficient contractility in the left ventricle, the history of IE and the lack of any benefit to sugical correction [24] or balloon valvuloplasty [22]. The AR was medically treated with amlodipine, because the afterload reduction may reduce the AR severity [15]. However, the afterload reduction may worsen AS, though the AS severity did not siginificantly change in this particular case

after administering amlodipine. The PDA was ligated with non-absorbable surgical braided ligature and tape, because the braided ligatures were stronger than monofilament ligatures, a factor that appears to be essential for ligation of the large ductus arteriosus. However, braided sutures are not recommended for ductus arteriosus ligation, especially in dogs with IE, because the material is more prone to infection than are monofilament sutures [7].

Although reverse remodeling is usually observed in dogs that undergo PDA occlusion [31], there was no improvement in cardiac size after surgical correction of the PDA in the present case. Factors that may adversely affect reverse remodeling include older age at PDA closure, myocardium failure following long-term volume overload and residual shunt [31]. In addition, it has been reported in humans that AR may occur after ductus arteriosus occlusion due to disappearance of the large shunt flow and geometric changes in the aortic root [3]. In dogs with PDA, the increased diastolic pressure in the aorta following ductus arteriosus closure may worsen AR [19]. The AR may have worsened postoperatively in this case, because the AR peak velocity was extremely high and its PHT was short at immediately after surgery. Therefore, the worsened AR may have hindered reverse remodeling. The left ventricular diameter gradually decreased postoperatively, perhaps because the AR improved, indicated by the decreased peak velocity and increased PHT of AR. However, the significant reduction in shunt flow following ductus arteriosus closure may also be important in promoting reverse remodeling as the LA enlargement was completely resolved postoperatively.

PDA is one of the most common congenital heart diseases in dogs. In humans, PDA patients have a high risk of IE, which significantly decreases or disappears after complete or incomplete PDA occlusion [10, 30]. In addition, aortic-valve infection is extremely rare, even in humans with PDA. Aortic-valve infection due to IE has a poor prognosis in dogs. However, PDA correction should be decided according to the clinical status and response to medical treatment. Indeed, despite the presence of a slight residual PDA shunt, the dog in this report showed excellent clinical outcomes on long-term follow-up after PDA correction without recurrence of the IE or heart failure. There is no known previous report of a dog with concurrent PDA and IE, despite the reported risk of IE in dogs with PDA. This is the first report describing a dog with concurrent PDA and IE; however, the relationship between PDA and IE was not confirmed. Any association should be confirmed on postmortem examination as in humans, ductus arteriosus and left pulmonary artery lesions commonly affected by IE [9, 29] could not be detected by echocardiography [34].

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