NOTE

Surgery

Surgery for partial atrioventricular septal defect with pulmonary hypertension in an adult dog

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ABSTRACT. A 4-year-old, 5.9-kg female Japanese Spitz presented with syncope and exercise intolerance. Echocardiography revealed an ostium primum atrial septal defect (ASD), a cleft mitral valve, mitral valve regurgitation (MR), and tricuspid regurgitation (TR) (velocity: 3.6 m/sec, pressure gradient: 52 mmHg), leading to a diagnosis of partial atrioventricular septal defect (AVSD) with moderate pulmonary hypertension (PH). Open-heart surgery using cardiopulmonary bypass was performed through right atriotomy. The cleft of the mitral valve was sutured with polypropylene and the AVSD was closed using an autologous pericardial patch fixed with glutaraldehyde. No postoperative pulmonary hypertensive crisis occurred. Shunting flow through the ASD, TR and PH had completely disappeared 2 months postoperatively; however, moderate MR persisted. The dog is still alive 5 years postoperatively without clinical signs.

KEY WORDS: atrioventricular septal defect, cardiopulmonary bypass, dog, pulmonary hypertension

Atrioventricular septal defect (AVSD), also known as endocardial cushion defect or atrioventricular canal defect, is a rare congenital heart disease in humans [5, 25]. AVSD is caused by failure of the dorsal endocardial cushion to fuse with the septum primum and close the ostium primum in the atrial septum during formation of the cardiac chambers [29]. AVSD is classified into complete, transitional, and partial forms. Complete AVSD is characterized by a septum primum atrial septal defect (ASD), a ventricular septal defect, and 1 abnormally formed atrioventricular (AV) valve with 5 leaflets [26]. On the other hand, partial AVSD is recognized by a cleft mitral valve and an ostium primum ASD but no ventricular septal defect [26, 29]. The transitional AVSD is an intermediate type between the partial AVSD and the complete AVSD.

Complete AVSD presents early in life and, without treatment, leads to pulmonary hypertension (PH), whereas the time to development of PH varies with partial AVSD [11]. Although surgical repair using cardiopulmonary bypass (CPB) is used as the primary treatment of AVSD, the presence of PH is a risk factor for postoperative pulmonary hypertensive crisis [16]. Surgical repair of partial AVSD has been reported in 4 dogs; however, all of these dogs were puppies and the 3 that survived had no or mild PH [2, 26, 29]. We are not aware of any successful surgical repair of partial AVSD complicated with moderate PH in an adult dog; hence, we report this case in which an adult dog underwent successful surgical repair of partial AVSD with PH.

A 4-year-old, 5.9-kg female Japanese Spitz was referred for evaluation of a heart murmur and suspected congenital heart disease detected before the age of 1 year. A comprehensive examination had not been conducted because the dog had been asymptomatic. However, as the dog matured, she began to show exercise intolerance and syncope, suspected to be due to a partial AVSD found using echocardiography by a veterinarian at a nearby medical clinic. The dog was referred to the University of Miyazaki for a definitive diagnosis and surgical treatment. On physical examination, body temperature was 38.6°C, heart rate was 120 beats/min, and respiratory rate was 120 breaths/min. Thoracic auscultation revealed a grade IV/VI systolic murmur at the cardiac apex.
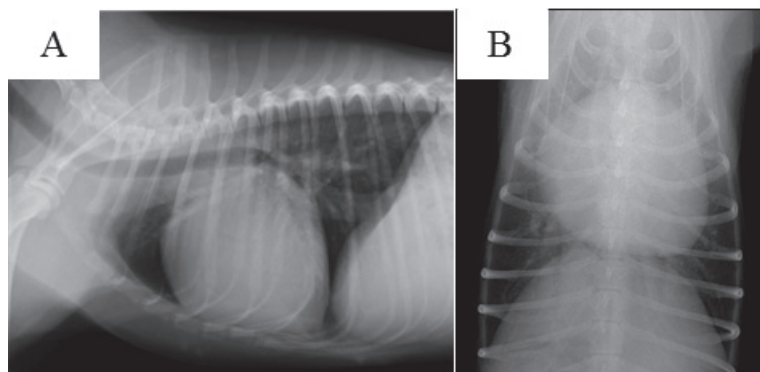
Fig. 1. Radiographic images of the thorax at the first visit. In the right lateral view (A), the vertebral heart score is 12.1. In the ventrodorsal view (B), the cardiothoracic ratio is 77.5%, indicating cardiomegaly.
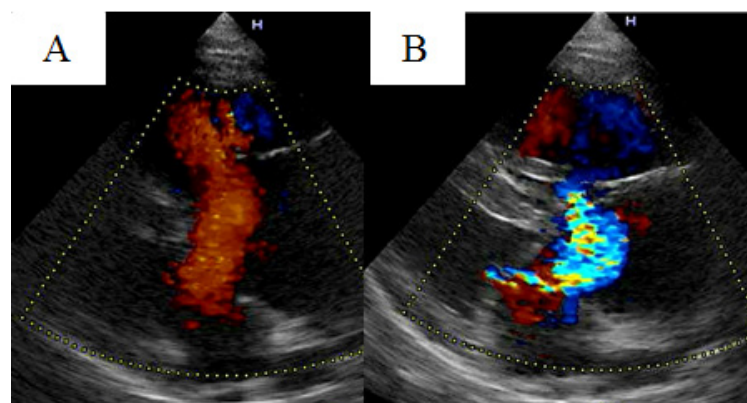

Fig. 3. Color-flow Doppler echocardiogram images obtained in the right parasternal long-axis view. In the diastolic phase (A), left-to-right shunting is observed through the atrial septal defect. In the systolic phase (B), mitral and tricuspid valve regurgitation are visible. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.
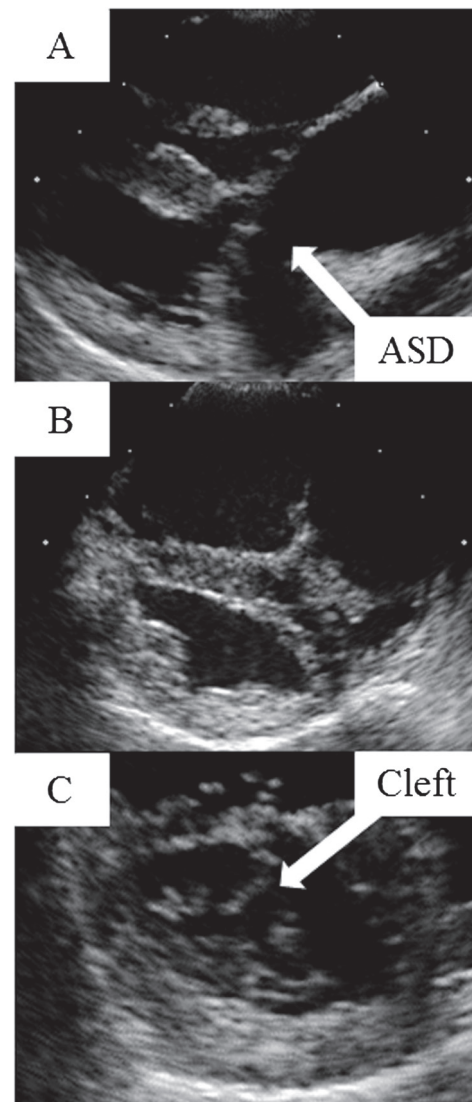

Fig. 2. Two-dimensional echocardiography images. In the right parasternal long-axis view (A), the atrial septal defect is visible immediately above the ventricular septum, and the right atrium and right ventricle are enlarged. In the right parasternal short-axis view at the level of the left ventricular papillary muscle (B), the interventricular septum is flattened. In the right parasternal short-axis view at the level of the mitral valve (C), a cleft is observed in the A2 segment of the anterior leaflet of the mitral valve. ASD, atrial septal defect.

Complete blood count, serum biochemistry, and blood coagulation test results were within the reference range. Electrocardiography showed sinus bradycardia (56 beats/min), wide QRS complexes, and a mean electrical axis of −92°. Thoracic radiography showed moderate cardiomegaly with a vertebral heart score (VHS) of 12.1 and a cardiothoracic ratio (CTR) of 77.5% (Fig. 1) [7]. The presence of enlargement of the right heart and pulmonary vessels suggested increased pulmonary preload.

Two-dimensional echocardiography revealed enlargement of the right atrium and ventricle. ASD was observed at the lower portion of the atrial septum, with a maximum diameter of 12.9 mm. Both left and right atrioventricular valves presented independent annuli, were anatomically separated and correctly located (Fig. 2A). The anterior leaflet of the mitral valve had a cleft (Fig. 2C). The interventricular septum appeared flattened, suggesting the presence of right ventricular pressure overload (Fig. 2B). The left ventricular end-diastolic diameter (LVEDd) was 21.6 mm, which was within the predicted reference limits (21.34–23.44 mm), but the left ventricular fractional shortening (FS) was 32%—below the reference range (33.7–45.9%) [6, 12].

Color-flow Doppler echocardiography indicated left-to-right blood flow across the ASD as well as mitral valve regurgitation (MR) and tricuspid valve regurgitation (TR) (Fig. 3). The peak velocity of the MR and TR jets was 5.26 m/sec and 3.60 m/sec, respectively. Although the dog had pulmonary regurgitation (PR) (the peak velocity was 2.80 m/sec), there was no echocardiographic evidence of subvalvular or valvular pulmonic stenosis. Since the right atrium was enlarged, it was defined as 10 mmHg. The estimated TR and PR gradients and right atrial pressure were then added to derive the estimated systolic and mean pulmonary

artery pressure, respectively. The estimated systolic pulmonary artery pressure was 62 mmHg, and the estimated mean pulmonary artery pressure was 41 mmHg. These estimated pressures in addition to the presence of syncope and interventricular septal flattening led to a diagnosis of moderate PH in this dog [18]. The pulmonary-to-systemic blood flow ratio (Qp/Qs) determined by stroke volume through the aorta, and the pulmonary artery systolic flow velocity integral was 2.9, which indicated increased right cardiac output with a left-to-right shunt [20, 32]. Based on the above-mentioned findings, the dog was diagnosed with partial AVSD with PH and surgical correction was recommended.

Preanesthetic medications included atropine sulfate (0.04 mg/kg subcutaneously), midazolam hydrochloride (0.3 mg/kg IV), and fentanyl citrate (5 μg/kg IV). Induction was achieved with propofol (4 mg/kg IV), after which the dog was intubated. General anesthesia was maintained with 0.5–2.0% isoflurane mixed with 100% O_2. After intubation, cefmetazole sodium (30 mg/kg IV), vecuronium bromide (0.1 mg/kg IV), and methylprednisolone sodium succinate (10 mg/kg IV) were administered. Positive-pressure ventilation was maintained throughout the anesthetic period except during total perfusion. Electrocardiography tracings, respiratory rate, rectal temperature, esophageal temperature, arterial oxygen saturation, end-tidal carbon dioxide concentration, and isoflurane concentration were monitored continuously during the surgery (Life Scope A, BSM-5192; Nihon Kohden, Tokyo, Japan). The left femoral artery was catheterized for the measurement of arterial pressure, arterial blood gas concentrations, complete blood counts, hematocrit, total protein concentration, serum biochemical parameters, and activated clotting time (ACT). The left femoral vein was catheterized for the measurement of central venous pressure (CVP). An 8 Fr polyethylene catheter was placed in the bladder and used for the measurement of urine output. CPB was conducted using an artificial heart–lung machine (Extracorporeal Circulation System; Jostra AG, Hirrlingen, Germany). The CPB circuit was filled with 20% D-mannitol (29 m*l*) (20% Mannitol YD; Yoshindo, Toyama, Japan), 8.4% sodium bicarbonate (12 m*l*) (Meylon 8.4%; Otsuka Pharmaceutical, Tokyo, Japan), 5% glucose (59 m*l*) (5% glucose solution; Otsuka Pharmaceuticals, Tokyo, Japan), and acetated Ringer's solution (300 m*l*) (Veen F; Kowa Pharmaceutical, Tokyo, Japan).To prevent a postoperative pulmonary hypertensive crisis, ventilation pressure was reduced and ventilation frequency was increased to avoid hypercapnia and hypoxia. In addition, low-dose milrinone lactate (0.5 μg/kg/min IV) was infused during and after the surgical procedure. Furthermore, cefmetazole sodium was administered every 2 hr and vecuronium bromide administered hourly during surgery.

Right thoracotomy was performed in the fourth intercostal space after administration of an intercostal nerve block using bupivacaine hydrochloride. After thoracotomy, the pericardium was incised below the phrenic nerve and a patch graft large enough to close the septal defect was carefully harvested. The pericardium was then sutured to the chest wall to create a pericardial cradle. The autologous pericardium was immediately immersed in 0.625% glutaraldehyde solution for 3 min at room temperature and rinsed in 0.9% saline solution [19].

Subsequently, heparin sodium (300 U/kg IV) was administered. After heparinization (ACT >400 sec) [33], an 8 Fr CPB cannula (DLP Pediatric One-Piece Arterial Cannulae; Medtronic, Tokyo, Japan) was inserted into the right carotid artery for the arterial line of the CPB. A 12 Fr CPB cannula (DLP Malleable Single Stage Venous Cannulae; Medtronic) was also inserted into the right jugular vein for the venous line of the CPB. Additionally, a root cannula was inserted into the aortic root for the administration of a cardioplegic solution, while a 14 Fr CPB cannula (DLP Malleable Single Stage Venous Cannulae; Medtronic) was inserted from the incised right atrium into the caudal vena cava and connected to the intravenous line of the CPB. During CPB, the minimum perfusion flow rate was 50 m*l*/kg/min on the CPB pump, the minimum esophageal temperature was 21.3°C, and the anesthetic was switched from isoflurane to infusion of fentanyl citrate (0.4 μg/kg/min IV). The aorta was cross-clamped with vascular forceps, and cardioplegic solution (Miotecter; Mochida Pharmaceutical Co., Tokyo, Japan) (20 m*l*/kg at °C) was rapidly infused antegrade through the aortic root cannula to arrest the heart. Subsequently, the cardioplegic solution was administered at 20 min intervals at 10 m*l*/kg and 4°C.

An incision was made in the right atrium, and the ostium primum ASD was identified above the ventricular septum (Fig. 4A). The cleft located at the A2 segment of the anterior leaflet was continuous with the ASD. The separate parts of the mitral valve cleft were sutured with simple interrupted sutures using 5–0 polypropylene monofilament suture material (Nescosuture; Alfresa, Osaka, Japan). The septal defect was closed with the autologous pericardium patch fixed with 0.625% glutaraldehyde (Fig. 4B). The interventricular portion of the pericardium patch was sutured using 5–0 polypropylene with pledgets in the fibrous mitral annulus to avoid the risk of injury to the atrioventricular node (Fig. 4C). The rest of the patch was secured with a continuous suture using 5–0 polypropylene (Fig. 4D). The right atrium was closed with a simple continuous suture using 5–0 polypropylene after removing the 14 Fr CPB cannula from caudal vena cava. At the same time, the body temperature was raised, and dobutamine and dopamine infusions were started to prevent low cardiac output syndrome after surgery (both 2.5 μg/kg/min).

Air was completely extracted via the aortic root catheter. Following that, warm blood (30°C whole blood) was infused into the coronary artery via the aortic root catheter, after which the clamp was removed from the aorta. Ventricular fibrillation occurred when the heart started to beat spontaneously; therefore, electrical defibrillation was applied. As soon as a sinus rhythm was obtained, weaning from the CPB was instituted. After the hemodynamic parameters were stabilized, the CPB was completely discontinued, and the CPB cannulae in the carotid artery and jugular vein of the dog were removed. Aortic cross-clamping time and total CPB time were 110 and 185 min, respectively. Protamine sulfate was administered, and the thoracotomy was closed in a routine fashion. Inspired oxygen was gradually reduced to room air while monitoring blood gas parameters. The femoral artery and vein were then sutured with 7–0 polypropylene and the dog was extubated. The total duration of anesthesia (from intubation to extubation) was 420 min.

The dog was transferred to the intensive care unit with ongoing administration of fentanyl citrate (10 μg/kg/min) and propofol (0.1 mg/kg/min). About 10 hr after surgery, ventricular premature contractions occurred, warranting the administration of lidocaine
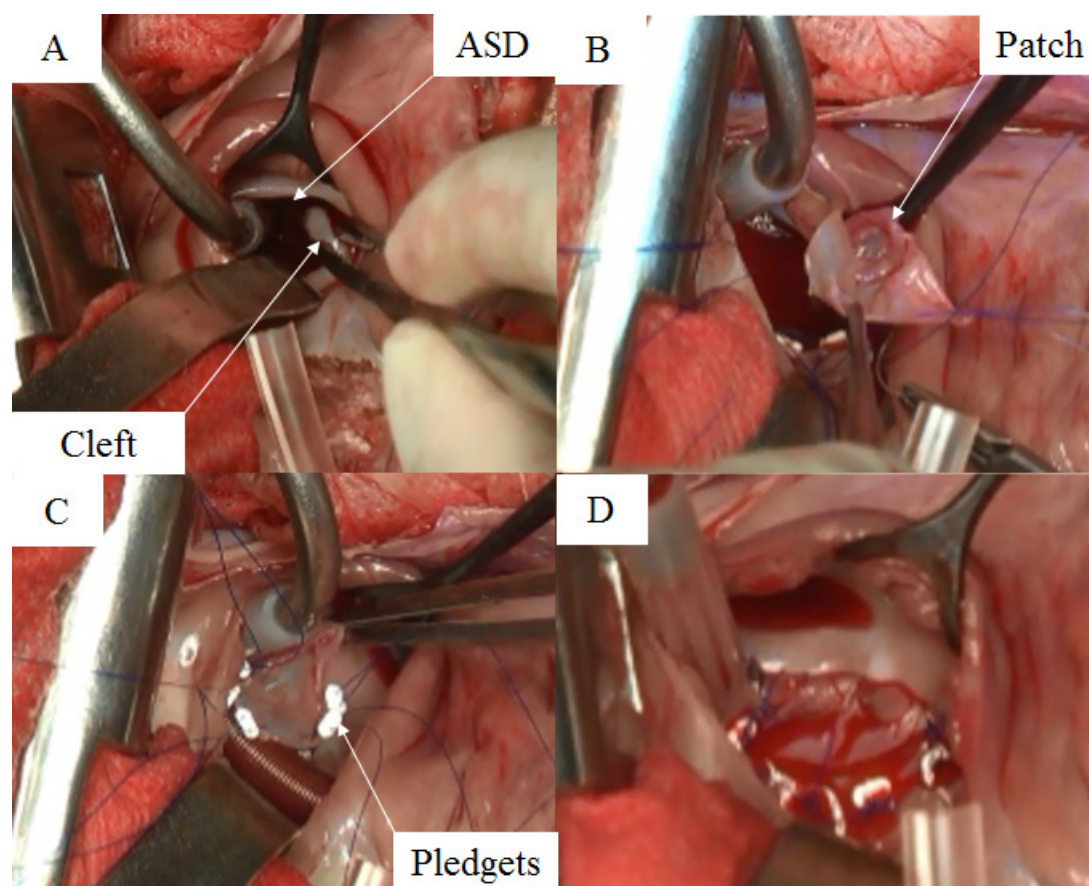
Fig. 4. Photographs taken during the surgery. (A) The right atrium has been opened, and the mitral valve containing a cleft is visible through the ASD. An autologous pericardial patch fixed with 0.625% glutaraldehyde (B) is used to repair the defect. The interventricular portion is sutured using polypropylene with pledgets in the fibrous mitral annulus (C), while the remaining portion of the patch is secured with a continuous suture (D). ASD, atrial septal defect.

(25–50 μg/kg/min) for 2 days. Cefmetazole sodium (30 mg/kg IV, every 8 hr) and dalteparin sodium (75 U/kg subcutaneously, every 8 hr) were administered for 6 and 4 days, respectively, after surgery. Since there were no findings of disseminated intravascular coagulation and intracardiac thrombus, administration of dalteparin was completed in 4 days. The dog started to eat 2 days postoperatively and had no clinical symptoms. The dog was hospitalized for 12 days due to the schedule conflict of its owner who lived far from our hospital.

Table 1 shows presurgical changes in the cardiovascular parameters until 2 years after the surgery. The dog remained in hospital for 12 days, during which time thoracic radiography revealed reduced heart size (VHS: 11.5, CTR: 65.6%) and echocardiography revealed residual—although decreased—blood flow through the ASD. Furthermore, TR and Qp/Qs were decreased to 2.4 m/sec and 0.89, respectively, and FS was increased (52%). However, the volume of residual MR flow, peak early diastolic velocity of the left ventricular inflow (E wave), and LVEDd showed increased values. Moreover, the concentration of plasma N-terminal pro-brain natriuretic peptide (NTproBNP) was still high, and the concentration of plasma atrial natriuretic peptide (ANP) had increased. Therefore, furosemide (1 mg/kg orally, twice daily) was administered for 3 days. The dog had no serious complications during hospitalization.

There was no evidence of TR or transseptal flow 2 months postoperatively (Fig. 5A and 5B). However, the E wave (1.33 m/sec) and E/E′ (33.5) values were greater than the predicted reference limits [35], and the LVEDd (32.8 mm) was markedly increased. Significant increase in systemic blood flow (LVSV) was caused by the increase in left ventricular preload (LVEDd, E wave, E/A and E/E′) due to residual MR. In addition to the increase in LVSV, a lowered Qp/Qs was caused by the significant decrease in pulmonary blood flow (RVSV) due to the disappearance of shunt flow. One year later, the LVEDd and FS remained unchanged; however, the E wave and E/E′ values, as well as the plasma cardiac biomarker concentrations were reduced, and the Qp/Qs was normalized. The dog underwent thorough, regular examinations for 2 years postoperatively and is still alive 5 years after the surgery without clinical symptoms. The E wave and E/E′ values and the plasma cardiac biomarker concentrations had decreased, and the VHS was normalized.

The prognosis with medical treatment is not favorable in AVSD patients, and surgical repair is considered the most effective treatment [22]. In the veterinary literature, there are reports of repair of partial AVSD in 4 canine patients. Nakayama *et al.* report

Table 1. Changes in the echocardiographic parameters, radiographic heart size, and plasma cardiac biomarkers

	Preoperation	Postoperation immediately	2 month after surgery	1 year after surgery	2 years after surgery
Ecocardiographic parameters					
E wave (m/sec)	0.81	1.12	1.33	1.1	0.99
A wave (m/sec)	0.61	0.49	0.45	0.94	0.79
E/A	1.33	2.29	3.00	1.17	1.25
E/E'	3.69	*N.E.*	33.5	18.3	15.6
MR velocity (m/sec)	5.3	5.4	5.6	5.4	5.8
TR velocity (m/sec)	3.6	2.4	*N.D.*	*N.D.*	*N.D.*
LVEDd (mm)	21.6	25.4	32.8	31.2	31.7
FS (%)	32	52	46	41	44
LA/Ao	1.63	1.29	1.37	*N.E.*	1.31
LVSV (m*l*)	13.2	21	31	14.2	*N.E.*
RVSV (m*l*)	37.9	18.7	10.7	14.4	*N.E.*
Qp/Qs	2.9	0.89	0.34	1.01	*N.E.*
Radiograhic heart size					
VHS	12.1	11.5	11.3	11.6	10.4
CTR (%)	77.5	65.6	69	66.7	65.1
Plasma cardiac biomarkers					
ANP (*pg*/m*l*)	75.9	144	86.6	38.5	9.7
NTproBNP (pmol/*l*)	2,341	2,152	>3,000	2,379	1,628

E wave, peak early diastolic velocity of left ventricular inflow; A wave, peak velocity at atrial contraction; E′, peak early diastolic velocity of the mitral annulus; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; LVEDd, left ventricular end-diastolic diameter; FS, fractional shortening; LA/Ao, a ratio of left atrial diameter to aortic root diameter; LVSV, left ventricular stroke volume; RVSV, right ventricular stroke volume; Qp/Qs; pulmonary-to-systemic blood flow ratio, VHS, vertebral heart score; CTR, cardiothoracic ratio; ANP, atrial natriuretic peptide; NTproBNP, amino-terminal pro-brain natriuretic peptide; *N.E.*, not examined; *N.D.*, not detected.
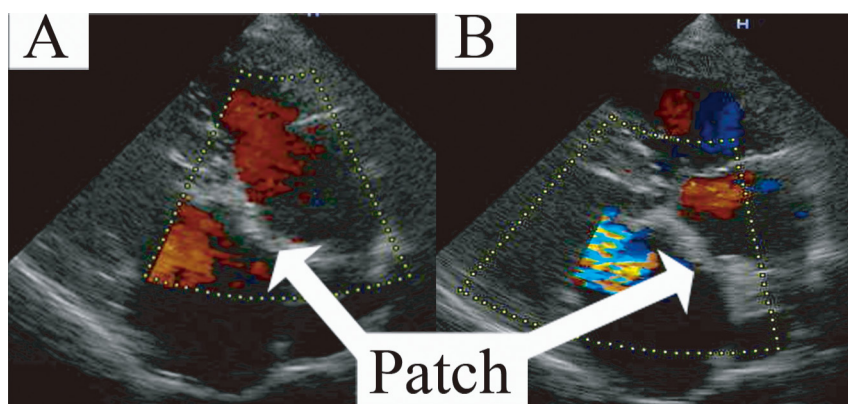

Fig. 5. Color-flow Doppler echocardiogram images at 2 months after the surgery. In the diastolic phase (A), the patch occludes the defect and left-to-right shunting flow is not observed. In the systolic phase (B), tricuspid regurgitation is absent, but mitral regurgitation persists.

repair of a partial AVSD in a dog under cross-circulation cardiopulmonary bypass, but the dog died 33 hr after the surgery [29]. On the other hand, Monnet *et al*. [26] and Akiyama *et al*. [2] report a successful repair using CPB in 2 cases and 1 case, respectively. However, the patients in these cases were all puppies younger than 1 year of age. To date, there are no reports on surgery for partial AVSD in an adult dog. Here, we describe the successful repair of a partial AVSD with PH in an adult dog.

Most human patients with partial AVSD have no symptoms in childhood, but tend to develop PH and right-sided heart failure as they get older. Patients undergoing surgery for congenital heart disease with PH have a high mortality because of the possibility of postoperative pulmonary hypertensive crisis [37]. Pulmonary hypertensive crisis is characterized by an acute increase in pulmonary pressure, with resultant overload of the right ventricle and decreased cardiac output. In 20 young children who underwent surgery for congenital heart disease with PH, 55% had 1 or more pulmonary hypertensive crisis and more than half of these died [16]. Supportive therapeutic treatment include 100% oxygen supply [17] and hypocapnia with low ventilation pressure and high ventilation frequency [27] to prevent constriction of the pulmonary artery during anesthesia. Additionally, low-dose intravenous milrinone was administered during and after the operation to reduce the pulmonary artery pressure. Milrinone, a selective inhibitor of phosphodiesterase III, has been shown to decrease pulmonary vascular resistance and pulmonary artery pressure in experimental

dogs with PH [9, 34]. To prevent pulmonary hypertensive crisis after cardiac surgery, inhaled nitric oxide and inhaled prostanoids are used frequently in human patients [3, 24]. However, the use of inhaled nitric oxide has been limited due to the toxic byproducts [10]. The use of inhaled prostanoids may also induce an adverse effect that is acute bronchoconstriction [1]. Several studies indicated the effect of milrinone on the pulmonary vascular bed as well as synergistic effects with inhaled prostanoids [4, 8, 21]. Milrinone can decrease rebound PH after inhaled nitric oxide is discontinued [36], and can enhance pulmonary vasodilation of PH in infants refractory to inhaled nitric oxide [23]. We could not assess the effect of milrinone administration on pulmonary artery pressure in our patient since the catheter examination was not performed to avoid the mechanical stimulation to pulmonary artery. However, the milrinone administration may contribute in the prevention of a pulmonary hypertensive crisis in light of the above reports. The application of these therapeutic measures could have helped prevent postoperative pulmonary hypertensive crisis in our patient.

Various methods are used for closure of ASD in human medicine. Of these, catheter occlusion has become widespread recently [13, 31]. In the present case, the AVSD anomaly could not be occluded by commonly used devices because the ostium primum ASD was located in a lower position of the atrial septum immediately above the ventricular septum. Closure with simple mattress sutures would have been straightforward; however, this method might have resulted in damage to the heart conduction system. Additionally, the defect orifice in the present case was too large to close directly. Patch grafts (equine or bovine pericardial xenograft, synthetic material and autologous pericardial patches) are often used to cover a defect orifice. In comparison to synthetic materials, autologous pericardial patches are cheap, nonporous, biocompatible, resistant to infection and thrombus formation, and are readily available. The use of fresh pericardium has its disadvantages including fibrous retraction, difficulty with surgical manipulation, and the possibility of aneurysm development with the growth of the patient [15]. For these reasons, the septal defect in this case was closed using an autologous pericardium patch fixed with glutaraldehyde. Although severe short-term calcification of glutaraldehyde-preserved patches have been reported [14], it did not occur in this case for 2 years after the surgery. Furthermore, small gaps were formed between the pericardium patch and the atrial septum, so the residual flow through the gaps was observed immediately after the operation. Two months later, however, the residual flow had disappeared.

In the present case, moderate MR persisted through the mitral valve cleft as a postoperative complication, and the increase in left ventricular preload was observed from cardiac biomarkers and echocardiographic parameters: LVEDd, E wave, E/A and E/E'. Postoperative residual MR is a major problem in human medicine, and this is the most frequent indication for reoperation following partial AVSD repair [28, 30]. Postoperative residual MR was also observed in the 3 dogs that underwent successful repair in previous reports; 2 with mild or moderate MR had no clinical symptoms, while 1 with severe regurgitation developed exercise intolerance and syncope [2, 26, 29]. A marked increase in the LVEDd was observed in the latter case [26]. Although the LVEDd of the present case was greater than the reference range, the dog showed no further increase in the LVEDd but exhibited a gradual reduction in left ventricular preload, and was asymptomatic for 5 years postoperatively. This case supports the need for regular examination to predict prognosis.

A major limitation of our report is the lack of cardiac catheterization. Cardiac catheterization allows the measurement of intra-cardiac pressure as well as the evaluation of the direction of blood flow (presence of right and left shunt). It also allows morphological assessment with angiography. However, the catheterization in dogs must be performed under anesthesia and the anesthetic effect on the hemodynamics cannot be ignored. Since most anesthetics have a hypotensive effect, the pulmonary artery pressure is underestimated. This underestimation is very dangerous for surgery. Moreover, since we predicted that the surgical procedure in this case would take a long time, the duration of anesthesia was expected to be extended further when cardiac catheterization was performed. Prolongation of the duration of anesthesia influences recovery after surgery. Furthermore, catheterization of the right side of the heart is not necessarily safe since catheter stimulation of the pulmonary artery can lead to a pulmonary hypertensive crisis. Additionally, since we could have sufficiently evaluated the hemodynamics with echocardiography, cardiac catheterization appeared to have little benefit. For the above-mentioned reasons, we concluded from a risk-benefit analysis that cardiac catheterization was not ideal in this case.

A partial AVSD with PH was diagnosed in an adult Japanese Spitz on echocardiography and cured by surgical repair with CPB. The ostium primum defect was covered with a pericardium patch fixed in glutaraldehyde solution and was closed completely 2 months postoperatively. At the same time, TR had completely disappeared. Although moderate MR persisted, the dog was asymptomatic without medical treatment for 5 years after the surgery. To the best of our knowledge, this is the first report of a surgical repair of partial AVSD with moderate PH in an adult dog.

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