Patent Ductus Arteriosus in the Canine Patient

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Introduction

Patent ductus arteriosus (PDA) is recognized as the most common congenital heart defect in dogs, accounting for 25-30% of congenital cardiovascular abnormalities.[1] The ductus arteriosus is a necessary structure in the fetal heart that allows blood to bypass the unoxygenated lungs. Failure of ductal closure at birth results in a patent ductus arteriosus, which can lead to volume overload of the left heart. This can progress to congestive heart failure and in some severe cases, Eisenmenger's syndrome. Presentation, diagnosis, treatment and prognosis of a PDA are dependent upon multiple factors including degree of ductal smooth muscle hypoplasia, size and shape of the ductus, directionality of blood flow through the ductus, and duration of the shunt. Diagnosis of PDA can often be made by physical examination and plain radiography alone; however, echocardiography, electrocardiography, and angiocardiography are often indicated for confirmation of the diagnosis and to aid in treatment planning. Medical therapy is rarely successful for the treatment of a left-to-right PDA in dogs, and surgical ligation or non-invasive occlusion is almost always recommended. Occlusion or ligation of the PDA is of imminent importance, as 65% of dogs will die from the development of congestive heart failure by 1 year of age.[2]

History and Presentation

Early epidemiological studies suggested a genetic component to the occurrence of PDA. Confirmation of genetic transmission came in 1971 when Patterson, et al. discovered the defect in a strain of toy and miniature poodles.[3] The inheritance pattern is described as a quasi-continuous or polygenic in that it is a threshold trait with graded phenotypic expression. The probability of a dog having a PDA and the degree of PDA severity are directly proportional to the amount of defective genome from the parents. Evidence has supported a two-threshold model

of inheritance. When the first threshold is met, a ductus diverticulum is formed, and the second threshold results in formation of a PDA. The lowest incidence of PDA occurrence is 20%, and results from crossing an unaffected dog with a dog that has a PDA. Intermediate inheritance of PDA is achieved when dogs with affected first-order relatives were mated with dogs that had ductus diverticula. An 80% incidence occurs when both parents have a PDA.[4] It has been documented that a genetic basis also exists in Welsh Corgis.[5]

The occurrence of PDA is three times more common in females than in males.[6] Other breeds over-represented in occurrence of PDA include toy and miniature poodles, Maltese, Pomeranians, Shetland sheepdogs, cocker spaniels, English springer spaniels, Keeshonden, Bichon frises, Yorkshire terriers, and collies.[4] The three breeds with the greatest odds of ductal patency are the Maltese, toy poodle, and miniature poodle.[7] The clinical presentation is dependent on the directionality, size, and duration of the shunt. Many dogs are asymptomatic at the time of diagnosis. PDA is most frequently discovered when a puppy presents for routine vaccinations, and the characteristic left basal continuous “machinery” heart murmur is ausculted during a thorough physical exam. Additional clinical signs associated with left-to-right shunts include mild exercise intolerance, stunted growth, hyperkinetic bounding pulses, and a palpable thrill over the left heart base. A palpable thrill may be absent in dogs with a small PDA. If clinical progression has reached left-sided heart failure, the associated clinical signs of severe activity intolerance, coughing, dyspnea, and exertional tachypnea may also be observed. Right-to-left shunting produces clinical signs consistent with deoxygenated blood delivery to systemic circulation, including severe exercise intolerance, pelvic limb collapse, and cyanosis of the caudal half of the body. The cranial half of the body is infrequently affected by cyanosis as the subclavian artery and brachycephalic trunks branch off the aorta and carry oxygenated blood to

the cranial half of the body prior to the location where the PDA shunts deoxygenated blood into the aorta for transport to the caudal half of the body.

Pathophysiology

The ductus arteriosus is an arterial canal that diverts approximately 80% to 90% of blood from the main pulmonary artery to the aorta, bypassing the nonfunctional fetal lungs.[6,8] Within minutes to hours after birth, this connecting vessel between the descending aorta and main pulmonary artery should close by smooth muscle constriction in response to increased oxygen tension. Inflation of the lungs at birth followed by thinning of the smooth muscle within the arterioles results in a decrease of pulmonary vascular resistance to 20% of systemic vascular resistance.[6] At birth, the loss of circulating placental-derived prostaglandins, in addition to the presence of oxygenated blood, decreases the inhibitory effect of the prostaglandins on ductal closure.[8] At this time, the increased oxygen tension at birth stimulates the ductus arteriosus smooth muscle to constrict and close. The process of non-inflammatory muscle degeneration, also known as “apobiosis”, produces a remnant of elastic fibers called the “ligamentum arteriosum”.[8] Failure of the ductus arteriosus to fully close in the immediate post-natal period results in the formation of a patent ductus arteriosus.

The wall of a normal ductus is comprised of 98% smooth muscle, with interspersed subadventitial elastic fibers and loose collagen making up the remaining 2%.[6] The distribution of muscle within a normal ductus is primarily circumferential, and in dogs with PDA, there is a greater proportion of non-contractile elastic tissue than smooth muscle tissue within the ductus. The combination of primary hypoplasia of the smooth muscle in addition to the secondary formation of elastic tissue is responsible for the failure of the PDA to fully constrict at birth.

Typically, the greatest amount of smooth muscle encircling the ductus is located at the portion adjacent to the pulmonary artery, and this results the characteristic funnel-shape of many PDAs.[4,6,8] A morphological grading system has been established with 6 degrees of histological ductus abnormalities based upon the amount of elastic tissue present within the normally muscular ductus wall. With increasing grade, the elastic tissue extends through a progressively greater percentage of the ductus circumference.[6] In grade 1, the elastic tissue is present in less than half the depth of the ductus wall, as compared to grade 2 that extends through greater than half. These grades are associated with a ductus diverticulum. Grades 3, 4, and 5 are associated with small, medium, and large PDA's, respectively.[6] A grade 6 ductus is completely lacking in smooth muscle, and results in a reverse, or right-to-left shunting, PDA.[8]

The volume of blood shunting across the PDA is directly proportional to the size of the ductus and the degree of pulmonary and systemic arterial resistance. In left-to-right shunts, the PDA continuously diverts a portion of the aortic outflow volume to the shunt circuit, which further includes the main pulmonary artery, pulmonary arteries, pulmonary veins, left atrium, and left ventricle, as long as systemic vascular pressure remains above that of the pulmonary vasculature. In addition to the right ventricular output volume, oxygenated blood shunting from the aorta into pulmonary circulation increases left ventricular, left atrial, and pulmonary venous pressures. This progression may lead to congestive heart failure or even generalized heart failure, especially in a grade 4 or 5 PDA. Left ventricular eccentric dilation and vessel enlargement is a common sequela, and rarely, hypertrophy of the pulmonary arterioles may result in pulmonary hypertension that reverses the flow of the shunt, a condition known as Eisenmenger's syndrome. A PDA must be corrected prior to reversal of the shunt, as ligation or occlusion is contraindicated in right-to-left shunting PDA. Occasionally, this shunt directionality is not a

result of worsening progression, but rather a persistently elevated pulmonary vascular resistance from birth.[9] The characteristic murmur is lost during reversal of the shunt, and the diagnosis of PDA is often missed without this indicator.

Differential diagnoses

Diagnosis of PDA is typically straightforward due to the pathognomonic presence of the left basilar continuous murmur that is often accompanied by a palpable thrill. The exception to this rule is the presence of Eisenmenger's syndrome, in which the murmur is lost with shunt reversal. However, a murmur is present in most animals with congenital heart disease, and the various causes of such murmurs should always be considered in a differential diagnosis list. A murmur ausculted in the left basilar region is not limited to patent ductus arteriosus, but can also include pulmonic stenosis, subaortic stenosis, tetralogy of Fallot, and an atrial septal defect.[8] These murmurs are systolic in nature, whereas PDA is continuous. Hyperkinetic bounding pulses are also characteristic of severe aortic insufficiency, due to the diastolic runoff. It should raise the clinical suspicion for pulmonary-to systemic shunting defects when cyanosis is observed. With tetralogy of Fallot, the cyanosis is often generalized, in contrast to the differential caudal cyanosis most often observed with PDA. A PDA is often a concurrent congenital heart disease with tetralogy of Fallot. Closure of PDA is contraindicated if in conjunction with tetralogy of Fallot, as the dog relies on the PDA for increased pulmonary blood flow.[6-8]

Diagnostic Approach/Considerations

Thorough physical examination with careful and complete thoracic auscultation is vital for the diagnosis of a PDA. The presence of a heart murmur or other characteristic clinical signs warrants further diagnostic investigation. The "machinery" murmur characteristic of PDA can

often be ausculted throughout the thoracic cavity, is often accompanied by a palpable thrill, and when loudest can be ausculted without a stethoscope. Quieter murmurs can be ausculted at the third intercostal space near the region of the heart base, which is the point of maximal intensity. A systolic murmur may be present in high-grade PDAs with bidirectional flow through the ductus, resulting from equalized pulmonary and systemic pressures. Murmurs with right-to-left shunting can produce a diastolic murmur or a split second heart sound, or no murmur may be present.[9-11] Large shunts can produce a systolic murmur in the region of the left cardiac apex, resulting from mitral valve regurgitation secondary to annular dilation.[8]

Thoracic radiographs are often the next step when performing diagnostic evaluation of a dog with a suspect PDA. The classic radiographic sign is viewed on the dorso-ventral projection as a lateral aneurysmal bulge of the aorta, which can be visualized at the level of the main pulmonary artery. Additional radiographic changes include a progressive enlargement of the left atrium, left ventricle, aortic arch, and pulmonary arteries. The cardiac silhouette often appears elongated due to these changes and can cause dorsal elevation of the trachea. Severe cardiac enlargement displaces the heart into the right hemithorax.[6] Enlargement of the pulmonary vessels and pulmonary edema may also be radiographically evident.[8] The presence of pulmonary over-perfusion is assessed by comparing pulmonary artery width to pulmonary vein width as they cross over the ninth rib.[2]

Electrocardiography (ECG) on lead II tracing is employed to assess for arrhythmias and heart chamber enlargement. Characteristic ECG changes associated with PDA include tall R waves (left ventricular enlargement) and wide P waves (left atrial enlargement). Atrial fibrillation is the result of severe left atrial dilation from a long standing PDA, and its presence on ECG indicates a grave prognosis.[12]

Confirmatory diagnosis of PDA is achieved using echocardiography. This diagnostic identifies concurrent congenital heart defects, commonly pulmonic stenosis, determines procedural feasibility for coil embolization and surgical ligation, and evaluates cardiac wall thickness and chamber size.[8] The ductus is visualized best in the right parasternal short axis basilar view and left cranial parasternal long axis view of the pulmonary artery.[13] Measurement of the ductus occurs at both extremities of the PDA. Color flow Doppler echocardiography shows continuous turbulent blood flow shunting into the pulmonary artery and may reveal presence of mitral valve regurgitation. Continuous wave Doppler measures aortic to pulmonary artery pressure gradient, which contributes information about pulmonary hypertension.[8]

Angiography is useful to predict the potential for procedural success prior to non-invasive occlusion of the PDA. This is performed just prior to ductal occlusion and is accomplished via the femoral artery by direct cut down. Pulmonary arterial pressure, intraductal pressure, and aortic pressure can be recorded. Ductal diameter can also be measured with a calibrated radiopaque ruler that is placed under the patient for simultaneous visualization with the patient.[14] Ductal morphology in dogs is classified according to angiographic appearance as type I, IIA, IIB, and III. Approximately one-half of affected dogs fall under the IIA classification due to the commonality of a funnel-shaped ductus. Type III represents a tubular-shaped ductus and is the least common classification.[7]

Treatment and management options

Correction of a PDA should be performed as soon as possible to avoid progression to congestive heart failure and avoid development of pulmonary hypertension. Medical management has been described in humans; however, it has not proven to be effective in canines. Dogs presenting with congestive heart failure should be stabilized with medical management

prior to correction of the PDA. If pulmonary edema is visible on radiographs, it is essential to treat with a diuretic for 24 to 48 hours before surgery or coil embolization.[4,6] Traditional therapy in canine patients has been surgical ligation via thoracotomy; however, attractive non-invasive occlusion techniques have proven to be safe and efficacious as well.

Surgical ligation of PDA in canines has been reported since 1952, and in the hands of an experienced surgeon the complication rate is less than 5%.[7] The standard left fourth intercostal thoracotomy approach provides adequate exposure of the surgical target. Once the PDA is confirmed by the presence of the palpable thrill, care is taken to preserve the phrenic nerve coursing across the heart and the vagus nerve coursing directly across the PDA. Meticulous dissection around the circumference of the PDA allows for passage of suture material. Once this is accomplished, the PDA is double-ligated, with the portion adjacent to the aorta being ligated first. At this time, the increased aortic pressure produces the "Branham reflex," characterized by a sudden onset of bradycardia. Successful ligation is determined by the absence of a continuous murmur. Additional post-operative complications include laryngeal dysfunction, air embolization, central nervous system hypoxia, myocardial hypoxia, hypothermia, and hypercapnea or hypocapnia accompanied by acid/base derangements.[15] The most common intraoperative complication of surgical PDA ligation is rupture or tear of the ductus resulting in catastrophic hemorrhage. Fatality rates increase to 42%-100% with this complication. Hemorrhage was reported in 6.25% of 64 cases in one study.[16] Surgical ligation is recognized as a highly successful procedure that is available for correction of all ductal morphologies and sizes.

Intravascular occlusion techniques involve the placement of thrombogenic coils or a single duct-occluding device. Among the various minimally invasive per-catheter-delivered

devices, embolization coils have been studied the most extensively.[7] Angiography characterizes the morphology of the ductus to determine if coil placement will be successful, and additionally to select the size of the coils to be placed. The predominant funnel-shaped morphology is desirable for this procedure, as the progressive narrowing at the end adjacent to the main pulmonary artery allows the detachable spring coils to become lodged. The mandril delivery wire advances the coils via the femoral artery into the PDA with fluoroscopic guidance. The mandril is withdrawn, allowing the coil to extrude into its helical shape, and if satisfactory coil placement is achieved, the guide wire is retracted. Additional coils are placed until resolution of the murmur is confirmed.[14] This procedure is less invasive than surgical ligation, and recovery time spans approximately 24 hours. A recent comprehensive study reported procedural and peri-procedural mortality to be 2.4%. Complications and procedure abandonment occurred in 11% predominantly due to coil instability and aberrant coil migration[7]. Outcomes with embolization coils are improved with smaller ductal diameters, as evidenced by a large human study where increasing ductal diameters and tubular shape were directly associated with unfavorable outcomes.[17] This procedure should be reserved for angiographically classified type II PDA's with minimum ductal diameters less than 2 mm. Advantages include the short hospitalization time and less discomfort for the patient. Radiation exposure, in addition to the requirements of expensive radiographic equipment and a large inventory of coils, catheters and procedures, summarize the disadvantages of this technique.

Multiple forms of Amplatz® occluders designed for use in human medicine have been repurposed for use in canines. However, the most recent device for minimally invasive per-catheter PDA occlusion in dogs is the Amplatz Canine Duct Occluder (ACDO), a self-expanding multilayered nitinol mesh device. It is also accomplished via a femoral artery approach. The flat

distal disc deploys in the main pulmonary artery, the waist is engaged with the pulmonic ostium, and the cupped proximal disc is secured within the ductal ampulla.[18] Early studies report no procedural or peri-procedural mortality. Complete ductal occlusion is reported in 94% of cases.[18] In one study of 40 procedures, all were successful with no instances of procedural abandonment.[7] PDA occlusion is commonly immediate, complete, and permanent. The primary limitation with this device is the large diameter of the delivery systems. This procedure is also not attempted in dogs weighing less than 4 kg. It has thus far proven to be effective over a wide range of ductal morphologies and sizes, although minimal information with type III tubular morphology is available.[7] Correct measurement of the PDA and accurate device sizing is essential for procedural success. Overall, the ACDO appears to have surpassed previous devices with regard to ease of use, degree of closure, and decreased complication rate.[19]

Expected outcome and prognosis

The natural history of untreated PDA is limited to a study of 100 cases in which the defect was not occluded in 14 affected dogs. 64% of the untreated dogs died within 1 year of examination.[7] Early intervention with surgical ligation has proven curative if performed by 6 months of age, and earlier diagnosis and correction is correlated with decreased secondary changes.[5] One and two-year survival rates after PDA ligation are 92 and 87%, respectively.[20] Similar success has been realized with the minimally invasive techniques. A recent study reported an overall success rate of 92% for the transvascular occlusion techniques. Individually, the transarterial coil method and ACDO success rates were 86% and 98-100%, respectively.[19] After surgical closure or coil occlusion of the PDA, the presence of clinical signs, concurrent congenital heart disease, and severe mitral regurgitation within 24 hours of closure were associated with shorter survival times.[20] Surgical ligation is associated with increased major

complications, such as ductus hemorrhage, whereas the minimally invasive techniques are more frequently associated with minor complications.[21] Secondary changes are not entirely reversible; however, post-correctional improvements include a decrease in pulmonary vessel size by 1 week and reduction in cardiac size to normal within 3 months postoperatively.[6] The aortic aneurysm typically remains unchanged. With the eventual resolution of mitral regurgitation, the heart should auscult normally. For Eisenmenger's syndrome, the prognosis is improved as compared to untreated left-to-right PDA.

Conclusion

The failed closure of the fetal ductus arteriosus at birth is due to increased primary smooth muscle hypoplasia in combination with secondary non-contractile elastic tissue formation. This heritable histologic abnormality prevents symmetric constriction of the tubular ductus, resulting in a patent ductus arteriosus. Diagnosis begins with a thorough and complete physical examination, followed by thoracic radiographs and ECG, with echocardiography for confirmation of diagnosis and angiography for procedural planning. Although the safest and most effective method of PDA correction is yet to be determined, several options exist that yield favorable outcomes with low rates of complication.

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