Etiology of Patent Ductus Arteriosus in Dogs

James W. Buchanan
University of Pennsylvania, jwb@vet.upenn.edu

Donald F. Patterson

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Abstract
Patent ductus arteriosus (PDA) is the most common congenital heart disease in dogs and usually causes heart failure and death unless corrected at a young age. Previous histologic studies in a line of dogs derived from Miniature Poodles with hereditary PDA identified varying degrees of hypoplasia and asymmetry of ductus-specific smooth muscle and the presence of aortalike elastic tissue in the ductus wall sufficient to cause patency. To determine if similar structural abnormalities cause PDA in other dogs, serial-section, 3-dimensional histology of ductal architecture was studied in 8 non-Poodle purebred dogs with PDA with no immediate family history of PDA. Morphologic abnormalities were observed in 7 of 8 dogs with PDA and essentially were the same as those in dogs known to have a hereditary form of PDA. These findings suggest that apparently sporadic PDA in these breeds is caused by a genetic defect in the structure of the ductus arteriosus that is similar or identical to that in the Poodle. The relatives of dogs with PDA, particularly parents, offspring, and siblings, should be screened for evidence of PDA. Dogs with PDA should not be used for breeding, regardless of breed.

Keywords
Congenital heart disease, Heredity, Histopathology, Pathogenesis, Smooth muscle hypoplasia

Disciplines
Animal Diseases | Cardiology | Cardiovascular Diseases | Comparative and Laboratory Animal Medicine | Congenital, Hereditary, and Neonatal Diseases and Abnormalities | Veterinary Infectious Diseases

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Etiology of Patent Ductus Arteriosus in Dogs

James W. Buchanan and Donald F. Patterson

Patent ductus arteriosus (PDA) is the most common congenital heart disease in dogs. Clinical and pathologic aspects of the disorder have been summarized recently. Increased prevalence of PDA in certain breeds indicated that genetic factors were involved in the pathogenesis of PDA, and a mixed-breed–Poodle line of dogs with hereditary PDA was developed. Histopathology in dogs with hereditary PDA consistently identified abnormalities in the wall of the ductus arteriosus (DA) that explained failure of DA closure after birth. The DA was shorter than normal, the ductus muscle mass (DMM) was hypoplastic and asymmetric, and segments of the DA wall that should have been muscular instead had a noncontracting, aortalike elastic wall. Serial-section histology of fetuses predisposed to PDA identified 6 grades of abnormality characterized by asymmetrically reduced DMM and increased elastic tissue that correlated with increased PDA gene concentration in breeding experiments. To determine if similar morphologic abnormalities cause PDA in other dogs, serial-section histology was performed on 8 unrelated purebred dogs with PDA representing 7 non-Poodle breeds.

Materials and Methods

Eight cardiopulmonary specimens with PDA were obtained from the postmortem examination service or from dogs donated for study. Included were 2 Collies and 1 each of the Cocker Spaniel, German Shepherd Dog, Keeshond, Pomeranian, Shetland Sheepdog, and Shih Tzu breeds. Their ages ranged from 10 days to 3 months except for the Shetland Sheepdog, for which age was not recorded.

After gross examination and formalin fixation, each PDA and adjacent portions of the aorta and pulmonary artery were imbedded upright in paraffin so that the central part of the PDA could be sectioned transversely. The entire specimen was sectioned serially yielding 5–10 sections per slide and 50–150 slides per specimen. Every other slide was stained for elastic tissue to distinguish muscular and elastic elements. Selected additional slides were stained with hematoxylin and eosin or a pentachrome stain. Three-dimensional zone analysis was carried out and the distributions of muscle and elastic tissue in each of 5 zones of the DA were recorded (Fig 1). The results were compared with serial-section histologic studies in 55 healthy dogs and fetuses and 150 dogs and fetuses from a line of dogs with hereditary PDA.

Results

Healthy dogs had predominantly smooth muscle cells and very little elastic tissue throughout the wall of the DA, in contrast to the predominantly elastic tissue walls of the adjacent aorta and pulmonary artery. In the central zone (zone C in Fig 1), the DA separated from the pulmonary artery before it joined the aorta. The muscular tissue extended ventrally into the cranial wall of the pulmonary trunk (zone A in Fig 1) and dorsally into the ventral wall of the aorta (zone D) at least midway to the aortic opening (level 8 in Fig 1). In transverse sections, the DA wall had uniform thickness and smooth muscle cells were distributed evenly throughout the wall in the central zone (Fig 2). Intimal cushions commonly seen in other species were not observed. In affected fetuses and dogs with hereditary PDA, the DA joined the aorta before it separated from the pulmonary artery in transverse sections indicating, that the DA was shorter than normal. This observation was confirmed by counting the number of slides containing serial sections of the central zone. The smooth muscle in the DA wall was decreased in amount and distributed asymmetrically in a consistent, graduated manner. The muscular portion always was situated near the pulmonary artery and the thinner elastic portion always was adjacent to the aorta (Figs 3, 4).

Seven of the 8 dogs with sporadic PDA had histologic abnormalities of the DA wall similar to high-grade abnormalities (grades 4–6 in Fig 4) in the family of dogs with hereditary PDA. The DA was shorter than normal in all 8 dogs, and 7 dogs had asymmetric DMM. The DMM was maximal in zone B in the wall of the DA near the pulmonary artery. The wall of the DA adjacent to the aorta was thinner than the opposite wall, contained predominantly elastic tissue, and was noncontractile (Fig 5A–D). The noncontractile, elastic segments resembled the aorta and had more and thicker elastic lamellae and smaller cells with smaller nuclei and less cytoplasm than observed in mus-
Fig 1. Sagittal histologic section through the center of the ductus arteriosus (DA) and adjacent vessels in a normal newborn Greyhound. The smooth muscle of the DA is indicated by dotted lines and extends into the aorta (A) and pulmonary artery (P). Zone A is the portion of DA muscle in the cranial wall of the pulmonary artery proximal to the DA orifice between levels 1 and 2. Zone B traverses the wall of the pulmonary artery between levels 2 and 4. Zone C is the central region of the DA that is separate from the adjacent vessels between levels 4 and 6. Zone D is the segment of the DA that courses in the wall of the aorta between levels 6 and 8. Zone E is the portion of the aorta distal to the DA orifice that sometimes contains a small amount of ductal tissue between levels 8 and 9. Levels 3, 5, and 7 are arbitrary midpoints in their zones and are obtained by counting and halving the number of sections in the defined zones in each dog. Elastic stain; 15×. Modified from Buchanan.3

Fig 2. Transverse histologic section through the center of a normally constricted ductus arteriosus (D) in a 3-day-old mixed-breed dog. The ductus smooth muscle is uniformly distributed throughout the wall, mainly circumferential and contracted. The internal elastic lamina is fragmented and no intimal cushions are present. The aortic wall (A) and pulmonary artery wall (P) have thicker elastic fibers, and the cells have less cytoplasm. Elastic stain; 15×. Modified from Buchanan.3

Discussion

Normal DA closure requires a timely interplay of various morphologic, biochemical, molecular, and environmental factors, many of which are influenced by gestational age and consequent DA maturation and preparatory angiomalacia. Species differences also exist.3 Intimal cushions in the fetal DA that contribute to DA closure in humans do not occur in dogs.3 Instead, only minor postnatal intimal thickening occurs at the aortic and pulmonary artery ends of the DA in healthy dogs and serves to fill in the orifice depressions that remain after DA constriction. In dogs with PDA, a small amount of postnatal intraductal intimal thickening often develops over muscular segments of the wall (Fig 5).

The results of this study indicate that abnormal tissue architecture is the major cause of sporadic PDA in dogs, similar to what has been observed in familial, hereditary PDA in dogs. The shortness of the DA and incomplete encirclement of the DA lumen by muscle indicate that hypoplasia of the ductus muscle is the principal morphologic abnormality. The presence of elastic tissue in areas that should have been muscular is considered a secondary abnormality resulting from insufficient ductus muscle growth. If overgrowth of elastic tissue was the primary abnormality, it is probable that elastic segments would be thicker, the DA would be longer than normal, and the muscle-elastic interface would have an opposite contour.

Hypoplastic, poorly contracting muscle only in 1 side of the DA and interposed elastic tissue in the other side preclude effective sphincteric action when the muscular por-
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Fig 3. Transverse histologic section through the central region of the patent ductus arteriosus (PDA) (D), and adjacent vessels in an 11-day-old dog with hereditary PDA. The asymmetric ductus muscle (DM) is constricted and degenerating near the pulmonary artery (P). An intimal cushion (arrow) is present over the muscular segment. The thin, aortalike portion of the ductus wall (dotted brackets) adjacent to the aorta (A) is not constricted, has small cells, and contains thicker elastic fibers. The PDA is connected to both the aorta and pulmonary artery indicating that the ductus arteriosus is shorter than normal. Elastic stain; 25\( \times \).

Fig 4. Grading system for 6 degrees of hereditary patent ductus arteriosus abnormality based upon the extent of aortalike elastic tissue (shaded area) in the normally muscular ductus arteriosus (DA) wall adjacent to the aorta at level 6. In grade 1, the elastic tissue is present in less than half of the DA wall; in grade 2 it extends through more than half of the DA wall. In increasing grade abnormalities, the elastic tissue extends through progressively greater percentages of the DA circumference. The nonshaded muscular areas are progressively smaller. Modified from Buchanan.3

An increased risk of a specific congenital heart defect such as PDA in a particular breed, follow-up studies in the families of affected dogs or breeding trials usually have verified that the defect is genetic in cause.4,11 Statistically significant breed aggregations in clinic populations thus can be considered as strong evidence of a genetic cause, although definition of the mode of inheritance requires further study. The relatives of dogs with PDA, particularly parents, offspring, and siblings, should be screened for evidence of PDA. Dogs with PDA should not be used for breeding, regardless of breed.

In humans, PDA is common in premature infants with hypoxia associated with respiratory distress syndrome or immature DA structure and responsiveness.12,13 Spontaneous closure of PDA in these circumstances usually occurs when the infant matures to normal-term gestational age. Most histologic studies of human patients are based on neonatal PDAs in which DA tissue architecture appears normal.14 A few reports mention increased elastic fibers in older patients with PDA but note that this finding may be a result of altered hemodynamics over time.14–17 One study found increased elastic fibers in 8 of 20 PDA patients over 16 weeks of age but no excess elastic fibers in 22 younger patients with PDA.18 However, the investigators still maintained that the increase in elastic fibers probably was a primary congenital abnormality. No descriptions of ductus muscle hypoplasia, asymmetry, or specifically located elastic tissue were found.

Genetic factors are involved in some human patients with isolated PDA as well as hereditary skeletal syndromes but pathogenetic mechanisms have not been determined.19 The mechanism by which congenital rubella causes PDA in humans also has not been determined.20,21 One investigator reported that the ductus wall in infants with congenital rubella appeared immature.22 The rubella virus persists for months to years in tissues and causes decreased mitosis in most organs, resulting in decreased organ weights and low
Fig 5. Transverse histologic sections through the patent ductus arteriosus and adjacent vessels at level 6 in a 10-day-old Cocker Spaniel (A), 6-week-old German Shepherd Dog (B), 8-week-old Shih Tzu (C), and 12-week-old Collie (D). The aortalike portions of the ductus arteriosus wall (arrow, dotted brackets) adjacent to the aorta (A) are not contracted and contain thick elastic fibers. The asymmetric ductus muscle (DM) is contracted and degenerating near the pulmonary artery (P). Intimal thickening is present over the muscular segment in some dogs. Elastic stain; 25×.
Fig 6. Transverse histologic section at level 6 through a nonconstricted ductus arteriosus (DA) (D) in a 2-week-old Keeshond with a grade 1 DA abnormality. A focal area of subintimal elastic tissue (arrow) is present in the DA wall adjacent to the aorta (A). The DA muscle extends uniformly throughout the circumference and is not contracted. Pulmonary artery (P). Elastic stain; 15\( \times \)H11003.

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References


birth weights. Quantitative studies of ductal tissue in humans have not been reported, but hypoplasia of DA muscle may account for the occurrence of PDA in congenital rubella infection as it does in most dogs.