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Pathogenesis of Single Right Coronary Artery and Pulmonic Stenosis in English Bulldogs

James W. Buchanan

English Bulldogs are the most common breed to have pulmonic stenosis. Previous studies showed that this congenital heart abnormality in Bulldogs frequently is caused by a circumpulmonary left coronary artery originating from a single right coronary artery. Fetal anasarca also occurs often in Bulldogs and might represent congestive heart failure, but the cause is unknown. To determine if fetal anasarca is associated with a coronary anomaly and pulmonic stenosis, major coronary arteries were studied in 6 bulldog puppies with fetal anasarca. Five of the puppies had normal coronary arteries, and this led to the conclusion that fetal anasarca usually is not associated with major coronary abnormalities or pulmonic stenosis. The 6th puppy had single right coronary artery with circumpulmonary left coronary artery and moderate subvalvular pulmonic stenosis. Serial section histology suggests that the underlying cause of this syndrome is malformation of the left aortic sinus (of Valsalva) and inversion of the proximal segment of the left main coronary artery.

Key words: Cardiac pathology; Congenital heart disease; Dog; Embryogenesis; Fetal anasarca; Myocardial infarction.

Pulmonic stenosis is the most common congenital heart defect in English Bulldogs.[1] Recently, a distinct coronary artery (CA) abnormality was found in 3 Bulldogs and a Boxer with pulmonic stenosis.[2] Angiocardiography, surgery, and postmortem examination studies consistently showed a single right CA giving rise to a circumpulmonary left CA, which constricted the right ventricular outflow tract in a bandlike fashion at the level of the pulmonic valve (Fig 1). The association of these anomalies in Bulldogs was confirmed by others.[3,4] Many instances of single right or left CA in humans have been reported, but pulmonic stenosis in association with single right CA has not been observed.[5] The etiology of single CA has been hypothesized to be the result of failed development of the opposite coronary anlagen. The histopathologic finding of an abnormal left aortic sinus (of Valsalva) in a full-term Bulldog fetus with single right CA, as described in this report, support this hypothesis.

Fetal anasarca (generalized subcutaneous edema and pleural and peritoneal effusion) occurs often in Bulldogs (''water puppies''), but the cause is unknown.[6] To determine whether anasarca in stillborn Bulldogs might represent congestive heart failure caused by pulmonic stenosis and anomalous CA, gross and microscopic examinations were made of the hearts of edematous stillborn Bulldog puppies.

Materials and Methods

Six edematous Bulldog puppies were delivered by cesarean section or were stillborn from 6 different litters from different parents. The puppies were frozen or examined without fixation within 48 hours. Gross examinations of the hearts were made with a dissecting microscope. After formalin fixation, 2 hearts that appeared to be normal and 1 heart with abnormal CA distribution were examined histologically. The upper half of the hearts, including the 4 cardiac valves and major CA, were serially sectioned at 6 μm. Alternate ribbons of sections were stained with Van Gieson elastic stain and examined 3-dimensionally.[7]

Results

In 5 hearts, all valves and coronary arteries were normal on gross examination, and nothing abnormal was found in 2 hearts examined microscopically. In the 6th puppy, the size, weight, and shape of the heart were normal, but it had a single right CA, circumpulmonary left CA, and a hemorrhagic myocardial infarct involving the apex of the left ventricle. The right CA arose from the normal location. One millimeter distal to the right ostium, a circumpulmonary left CA, representing the left common CA, originated from the right CA and extended in the myocardium around the right ventricular outflow tract before trifurcating into the left circumflex, left cranial descending, and septal CA (Fig 2). The 3 fibrous commissures of the aortic valve were equidistant and appeared normal at their most proximal extent, but the commissures on either side of the putative left aortic sinus approached each other and fused in sections more distad. As a consequence, the left aortic sinus was smaller than normal and would have been difficult to identify grossly. In the left aortic sinus at the site where the left CA should have originated, an inward protrusion of elastic tissue was observed (Fig 3).

Discussion

CA distributions in dogs and humans are similar (Fig 1) except for two substantive differences. Dogs usually have a large septal CA originating at or near the left CA origins of the left circumflex and left cranial descending CA.[8] The septum in humans is usually supplied by several branches of the left cranial descending CA.[9] Dogs also have a left CA dominant distribution in which the caudal descending CA originates from the left circumflex CA. In humans, the caudal descending CA originates from the right CA 65% of the time.[9]

Most of the information on CA embryology in the lit-

From the Section of Cardiology, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA.

Reprint requests: James W. Buchanan, DVM, M Med Sci, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, 3850 Spruce, Philadelphia, PA 19104; e-mail: jwb@vet.upenn.edu.

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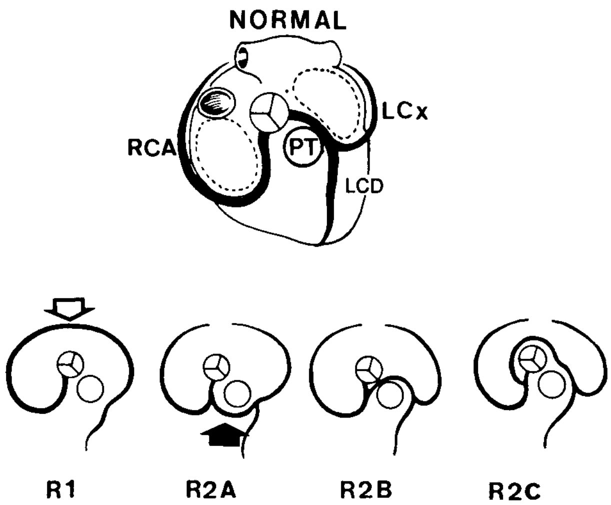

Fig 1. Diagram of normal coronary artery distribution in dogs and human beings and common patterns of single right coronary artery in the latter. In the type-R1 pattern, the right coronary artery (RCA) continues as a single vessel and crosses the caudal crux of the atrioventricular sulcus (open arrow), then continues as the left circumflex (LCx) and left cranial descending arteries (LCD). In type-2 patterns, the single vessel branches shortly after leaving the aorta. Subclassifications are made depending on whether the crossing vessel (solid arrow) passes cranial to the pulmonary trunk (R2A), between the aorta and pulmonary trunk (R2B), or caudal to the aorta (R2C). Reproduced with the permission of the American Veterinary Medical Association.[2]

erature comes from studies in humans. The major coronary arteries evolve from a plexus of subepicardial vessels that drain myocardial sinusoids communicating with the lumens of the right and left ventricles.[9] Blood enters the left ventricular sinusoids from the lumen and circulates through the subepicardial plexus before emptying into the venous sinus. The subepicardial plexus evolves into predominant coronary arteries around the atrioventricular groove and over the cranial and caudal borders of the interventricular septum. At this stage, a prominent circumpulmonary conal artery (circle of Vieussens, Vieussen's ring) may be present around the pulmonary outflow tract at the junction of the right ventricle and pulmonary trunk. The proximal segments of the definitive right and left CA develop independently by outward budding from the right and left aortic sinuses in the truncus arteriosus. These anlagen join the coronary arteries in the atrioventricular groove, and the circumpulmonary conal artery atrophies.

Histologic studies in this report indicate that proximal left CA development was abnormal in the puppy with single right CA. Growth and protrusion of a mound of elastic tissue into the left aortic sinus had occurred at the point where the left CA normally would extend outward. This observation suggests maldirection of the endothelial budding process from the truncus arteriosus during embryogenesis. No outward growth from the left aortic sinus was found. This finding supports the hypothesis that absence or maldirection of the left coronary anlagen causes development of a single right CA and persistence of the embryonic circumpulmonary conal artery that normally disappears in embryogenesis. The left aortic sinus also was small in the reported cases of single right CA and pulmonic stenosis.[2]

In the reported cases of single right CA and pulmonic stenosis, the circumpulmonary left CA was just external to the juncture of the right ventricular myocardium and the pulmonic valve root.[2] It constricted the pulmonic valve at the valvular level and was associated with hypoplasia of the pulmonary sinus adjacent to the aorta. In contrast, the circumpulmonary left CA in the affected puppy was intramyocardial in a subvalvular location until it became epicardial just before trifurcating into the left circumflex, left cranial descending, and septal CA. The right ventricular outflow tract lumen was moderately constricted under the circumpulmonary left CA (Fig 2). If this puppy had matured, the resultant pulmonic stenosis probably would have been classified as subvalvular pulmonic stenosis.

The heart weight and right ventricular wall thickness in the puppy with abnormal CA were similar to those of the other puppies, indicating that right ventricular hypertrophy (RVH) in response to outflow obstruction had not occurred. It is probable that the development of RVH in young Bulldogs with single right CA and clinically relevant pulmonic stenosis is equivalent to the hypertrophy that develops with growth in young dogs after banding the pulmonary artery. The absence of RVH in the abnormal puppy is evidence that the circulation was not impaired in utero and that the coronary anomaly was not the cause of fetal anasarca in this puppy or the other 5 puppies.

The etiology of the myocardial infarct in the left ventricle is uncertain. It probably was caused by compression of the intramyocardial segment of the circumpulmonary left CA in association with hemodynamic changes at parturition. Acute infarction of the left ventricle, hypotension, and death occurred in 2 reported dogs when the circumpulmonary left CA was severed at the time of attempted patch graft surgery to correct pulmonic stenosis.[2,3] Avulsion of the circumpulmonary left CA also was suspected as the cause of death in 2 Bulldogs undergoing balloon valvuloplasty for pulmonic stenosis.[4] Infarction and sudden death has been reported in humans with single right CA and a left main CA branch passing between the aorta and main pulmonary artery.[5]

Increased frequency of pulmonic stenosis in Bulldogs has been recognized[10] since 1960. A survey 30 years later indicated that this breed continues to have the highest frequency of pulmonic stenosis.[1] The relative risk for pulmonic stenosis in Bulldogs was 19 times that of all other breeds. Pulmonic stenosis in Bulldogs occurs occasionally

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Fig 2. **(A)** Histologic cross-section at the level of the right ventricular (RV) outflow tract of a stillborn fetus with single right coronary artery (R) just beyond the branch point of the circumpulmonary left artery (C). **(B)** Notice the circumpulmonary left artery (C) coursing in the myocardium around the RV outflow tract and compressing it. It becomes epicardial when it approaches the great cardiac vein (V) just before branching into the left circumflex (X), septal, and left cranial descending coronary arteries (not seen in this illustration). Van Gieson stain, 25×. Bar = 1 mm.

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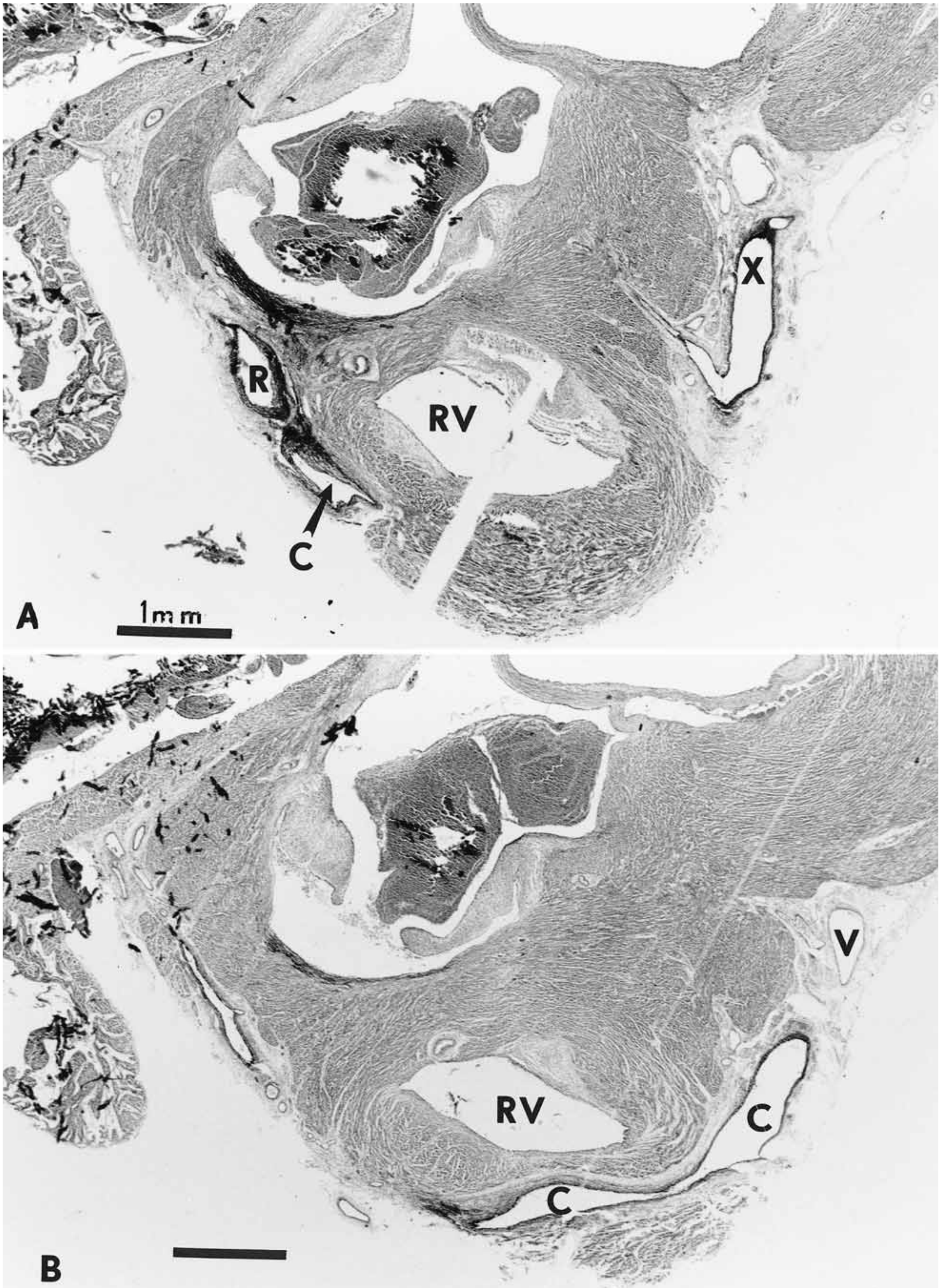

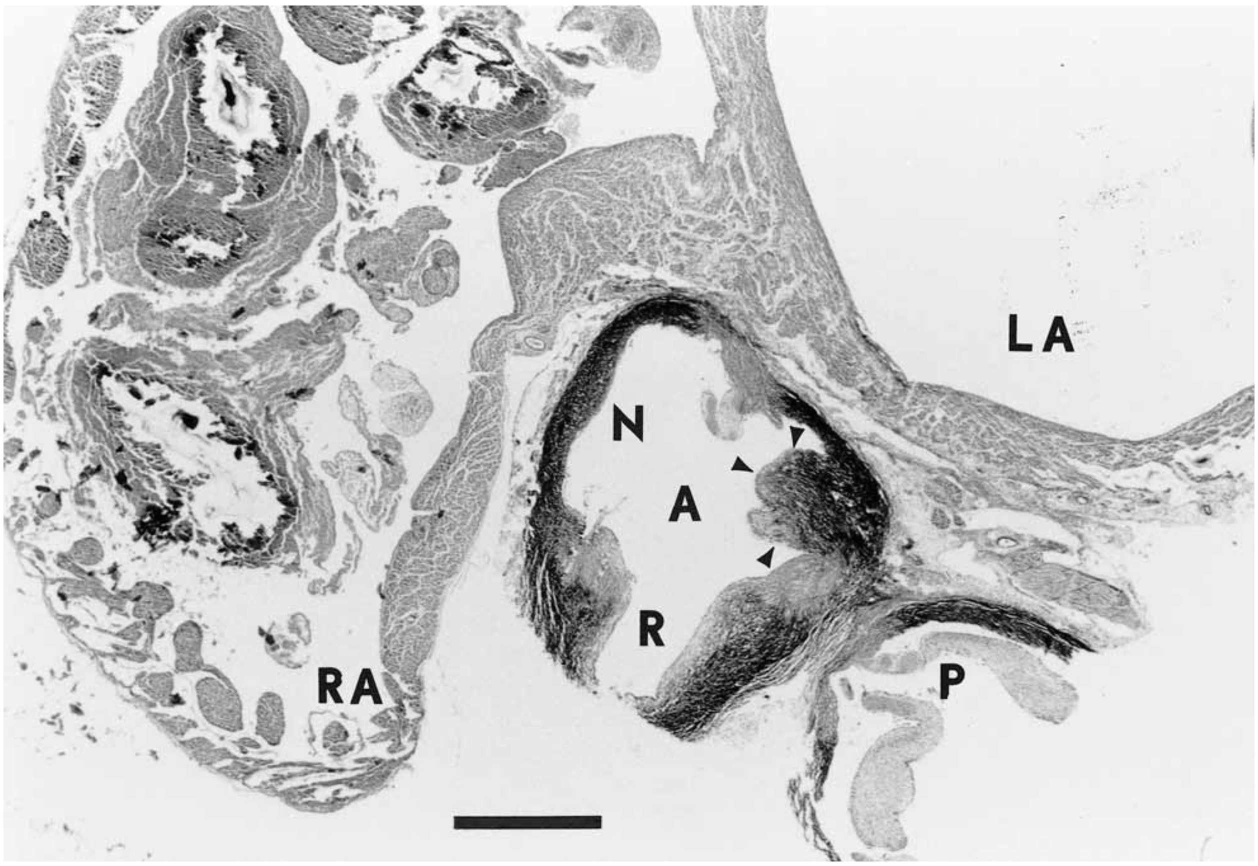

Fig 3. Histologic section of the heart base of the stillborn fetus with single right coronary artery and abnormal left aortic sinus of Valsalva. The right coronary sinus (R) and noncoronary sinus (N) are slightly larger than the left sinus and appear normal except for increased thickness of the wall of the right sinus. In the left sinus, notice the inward protrusion of elastic media (arrowheads) at a point where the left coronary artery should have extended outward from the aorta (A). Pulmonary valves (P). Right atrium (RA). Left atrium (LA). Van Gieson stain, 20×. Bar = 1 mm.

without single right CA, and when it does, the obstruction appears to have the same spectrum of morphologic types and locations seen in other dogs. However, in a recent tabulation of cases at the School of Veterinary Medicine of the University of Pennsylvania, 7 of 8 Bulldogs with pulmonic stenosis had single right CA. Reported cases from California, Japan, and Europe indicate that the propensity for single right CA exists in Bulldogs and that the CA anomaly may cause the majority of cases of pulmonic stenosis in this breed.

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