Multiple cardiac anomalies in a family of Saluki dogs.

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Multiple Cardiac Anomalies in a Family of Saluki Dogs

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Summary

Clinical studies of a family of Saluki dogs demonstrated a spectrum of cardiac malformations, which ranged from mild thickening of a pulmonary valve leaflet to a complex condition composed of tricuspid valve insufficiency, pulmonic stenosis, patent ductus arteriosus, and mitral valve insufficiency. All affected dogs had patent ductus arteriosus or ductus diverticulum, which is an incomplete or atypical form of patent ductus arteriosus. The clinical findings varied with the type of cardiac lesion(s) found. Pedigree evaluation suggested a genetic cause, though environmental factors could not be excluded.

Epidemiologic studies have shown that patent ductus arteriosus (PDA) and pulmonic stenosis (PS) are the most commonly observed cardiac malformations in dogs.1 Familial studies and controlled breeding experiments have subsequently confirmed that PDA in Poodles and PS in Beagles are polygenically heritable traits, as are subaortic stenosis in Newfoundland dogs, persistent right aortic arch in German Shepherd Dogs, and tetralogy of Fallot in Keeshondens.2,3

Congenital cardiac disease is usually found as a single lesion, but affected dogs occasionally have complex cardiac problems. In one study of a family of Keeshonden, hereditary defects of the conotruncal septum were identified as the major lesion, but lesions such as pulmonary stenosis, persistent left cranial vena cava, and absent ductus arteriosus also were associated with the primary abnormality.4 In Boxers, an unusual spectrum of cardiac defects was found; secundum-type atrial septal defects and aortic valvular stenosis occurred commonly, and a persistent right venous valve was identified in 3 dogs.4 This report deals with a family of Salukis that had cardiac defects similar in scope to those of the Boxers. The clinical features of these defects and their potential heritability are discussed.

Materials and Methods

The index case, dog 1, a 5-year-old female Saluki, was examined at the Comparative Cardiovascular Studies Unit, College of Veterinary Medicine, University of Minnesota. The examination revealed PDA and prompted the cardiovascular examination of many adult Salukis and pups from 4 genetically related litters.

For each dog examined, environmental factors varied. Breeding, gestation, and whelping histories were taken on all affected dogs.

Physical examination included auscultation and phonocardiography of the thorax, standard electrocardiography (ECG), and dorsosventral and lateral thoracic radiography.

Cardiac catheterizations were performed with the dogs under general anesthesia. Sodium thiopental was used for induction, and anesthesia was maintained on a combination of nitrous oxide and halothane gases. The left side of the heart was approached via left carotid or left femoral artery cannulation, utilizing either Lehman ventriculography or Gensini catheters.5 The right side of the heart was catheterized with a flow-directed pulmonary angiography catheter placed via left jugular or left femoral vein cannulation. Intracardiac pressures with simultaneous ECG and phonocardiograms were recorded with an 8-channel photographic recording oscillograph6 with matched transducers and amplifiers. Selective angiocardiograms were made with a cut film changer7 at a speed of 4 frames per second.

Results

Of the 46 dogs represented in the pedigree (Fig 1), 35 dogs were evaluated for heart disease. Of the 35 dogs examined, 15 had cardiac murmurs of grade II/VI intensity or greater. Six of the 15 were catheterized, and 2 of the 6 dogs catheterized were necropsied; the remaining 9 dogs could not be evaluated by other than physical examination and auscultation.

The cardiac anomaly most frequently encountered was PDA or ductus diverticulum. This lesion was observed in all 6 dogs catheterized. Three dogs (2 from the same litter), had evidence of pulmonic valvular thickening or stenosis. One dog had a complex disease composed of a tricuspid valvular anomaly, PS, PDA, and mitral valve insufficiency. Mitral valve insufficiency was observed in 2 dogs.

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2. Edwards Laboratories Inc, Santa Ana, Calif.

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Clinical Findings—The most prevalent clinical sign was a heart murmur. In 2 dogs, the clinical signs were those typically associated with PDA; however, dog 2 (with PDA, PS, tricuspid valve insufficiency) had complex signs and evidence of right-side heart failure.

Auscultation—In the 3 dogs with PDA, a continuous murmur was heard at the left thoracic wall. The point of maximal intensity for uncomplicated PDA is usually the left 3rd intercostal space. This was so in dogs 1 and 5, but the point of maximal intensity was at the left 5th-6th intercostal space in dog 2 because of extreme right atrial enlargement. In this dog, a grade IV/VI crescendo-decrescendo holosystolic murmur, best heard at the right 4th-5th intercostal space, was attributed to severe tricuspid valve insufficiency. The dogs with mitral valve insufficiency or ps with ductus diverticulum had murmurs typical of the valvular lesion. For the 9 dogs that had heart murmurs but were not catheterized, the maximal intensity of the murmurs was on the left side, over the mitral or aortic areas. The intensity of these murmurs ranged from grade I to III, of a possible VI. These findings suggested mitral or aortic valve involvement.

Electrocardiography—All dogs had at least 1 ECG abnormality, but the change(s) was not specifically characteristic of the major defect in every instance. Dogs 3 and 4 (with pulmonic valvular abnormalities and ductus diverticulum) had, respectively, ECG patterns of biventricular and left ventricular enlargement. The ECG from dog 2, which had tricuspid valve insufficiency as the major feature of disease, had a pattern of right ventricular hypertrophy, consistent with the major lesion. P wave changes indicating atrial enlargement were observed in dogs 1, 2, and 6. Only dog 5 developed an arrhythmia (unifocal premature ventricular contractions).

Radiography—Radiographic findings were usually indicative of the lesion: enlargement of the aortic arch, main pulmonary artery enlargement, left atrial and left ventricular enlargement in PDA; main pulmonary artery dilatation in pulmonary valve abnormalities; or left atrial and left ventricular enlargement in mitral valve insufficiency. However, dog 2 had an unusual radiographic pattern brought on by extreme right atrial enlargement (Fig 2).

Angiography—Selective angiographic studies of 5 of the 6 dogs studied led to the discovery of some defects not anticipated on preliminary physical examination. In dog 2, the PDA and tricuspid valve insufficiency that were expected from previous evaluations were corroborated (Fig 3). Mitral valve insufficiency and ps were additionally discovered. Two dogs (No. 3 and 4) with murmur typical of ps but which had ECG evidence of left ventricular or biventricular enlargement had an
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Fig 2A—Dorsal radiolograph of dog 2, showing marked cardiomegaly. Most of the increase in cardiac mass is due to right-

side enlargement, causing displacement of the left ventricular border to the left. Silhouettes of the aorta (A, arrows) and

pulmonary artery (PA) are within the silhouette of the heart. Notice the left shift of the cranial vena cava (CrVC) and the

displacement of the caudal vena cava (CVC).

B—In the lateral radiographic view, the trachea is markedly elevated by cardiomegaly. The aortic arch (arrow) is displaced dorsal

and cranial.

Fig 3A—Lateral selective angiogram of the right atrium of dog 2. One catheter has been placed in the left ventricle. The tip of the

other catheter (C) is directed toward the right auricle (RAu), which is filled with contrast medium. The total mass of the right atrium

(RA) is shown in outline by the arrows. Right ventricular (RV) and main pulmonary artery (PA) filling has occurred, and these

structures can be visualized faintly beneath the mass of the right atrium.

B—A dorsosventral view of the left ventricular (LV) injection better delineates the simultaneous filling of the aorta (A) and main

pulmonary artery (PA) caused by the PDA.

angiographic evidence of pulmonic valvular disease

(Fig 4), which resulted in a pressure gradient across

the pulmonic valve in dog 3. A ductus diverticulum

was observed in these 2 dogs (Fig 5) as well as in dog

6, which also had angiographic evidence of mitral

valve insufficiency.

July 1, 1981
Intracardiac Pressures—Intracardiac pressures were recorded in 5 dogs (Table 1). Though 3 of them (No. 2, 3, and 4) had evidence of elevated right atrial mean pressure, only one (dog 2) had evidence of venous congestion and peripheral fluid accumulation. Right ventricular-pulmonary artery pressure gradients were recorded in 2 dogs that had pulmonary valve lesions, but was not demonstrated in dog 4, though it had angiographic evidence of pulmonic valve thickening. Dog 4 also had an elevated aortic diastolic pressure (120 torr) and a high left ventricular end-diastolic pressure (15 torr). Two other dogs (No. 2 and 3) also had relatively high left ventricular end-diastolic pressures. Mild elevation in pulmonary artery systolic pressure was demonstrated in dogs 4 and 5.

Gross Pathologic Findings—The cardiovascular systems of dogs 2 and 5 were evaluated at necropsy. Dog 2 had ascites, subcutaneous edema, and pleural and pericardial effusion. The heart was markedly abnormal. Viewed from its ventral surface, there was right ventricular enlargement resulting in formation of a double apex and displacement of the left ventricle to the left and cranial. The left ventricle appeared small, when compared with the right ventricle. The heart was rotated clockwise approximately 45 degrees in both the craniocaudal and dorsoventral axis. The right atrium was greatly dilated; its external dimension was nearly equal to that of the remaining portion of the heart (Fig 6A). The right ventricle was hypertrophic and the large anterior papillary muscle inserted directly into the thickened and fenestrated nonseptal cusp of the tricuspid valve (Fig 6B). Two small, irregular papillary muscles also contributed single thickened chordae tendineae to the leaflet. The septal cusp was thick, and the papillary muscle of the conus inserted directly into its infundibular margin. The origin and position of the valve relative to the atrioventricular annulus appeared normal. The pulmonary valve cusps were all thickened, with slight fusion at the base of all cusps. The pulmonary artery

TABLE 1—Cardiac Catheterization Data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Intracardiac pressures in torr (mmHg)*</th>
<th>Lesions demonstrated by angiography†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RA = right atrium; RA = right atrial mean; RV = right ventricle; PA = pulmonary artery; PA = pulmonary artery mean; AO = aorta; LV = left ventricle.</td>
<td>PDA (physical examination)</td>
</tr>
<tr>
<td>2</td>
<td>18/8 12 35/12 22/15 19 95/70 95/15</td>
<td>PDA  PS MI</td>
</tr>
<tr>
<td>3</td>
<td>15/6 8 50/8 22/8 14 140/105 140/18</td>
<td>PDA  PS DD</td>
</tr>
<tr>
<td>4</td>
<td>10 10 40/15 38/16 22 105/120 170/18</td>
<td>PDA  PS DD</td>
</tr>
<tr>
<td>5</td>
<td>8/0 6 35/9 22/16 24 145/100 140/10</td>
<td>PDA  PS DD</td>
</tr>
<tr>
<td>6</td>
<td>3/0 2 24/2 22/10 16 136/88 140/10</td>
<td>PDA  PS DD</td>
</tr>
</tbody>
</table>

*RA = right atrium; RA = right atrial mean; RV = right ventricle; PA = pulmonary artery; PA = pulmonary artery mean; AO = aorta; LV = left ventricle. †PDA = patent ductus arteriosus; DD = ductus diverticulum; PS = pulmonic stenosis; MI = mitral valve insufficiency; TT = tricuspid valve insufficiency.
at necropsy, edema, and heart was ventral surface and displacement. The paired with clockwise ranicauad was greatly rly equal to that (Fig 6A). 

id the large tly into the cusp of the r irregular thickened tal cusp was ns inserted. The origin the atrio.

The pulmonary artery with slight ary artery

superior to the valve was dilated. An opening, 1 mm in diameter, was found at the pulmonary artery side of the ductus arteriosus (Fig 6C). A large diverticulum was at the aortic side, giving the ductus arteriosus a cone-shaped appearance. The foramen ovale was probe patent, but it was judged to be nonfunctional.

When dog 5 was 16 months old, it died of congestive heart failure secondary to PDA. The heart was rounded, with marked dilatation of the left ventricle and left atrium. The aorta was dilated at the site of the duct. The duct opening on the aorta was 5 mm in diameter. The duct entered the pulmonary artery at the bifurcation of the pulmonary artery branches. The pulmonary artery and its main branches were enlarged. The lungs were congested and edematous.

Discussion

The fact that specific forms of cardiac disease were identified in this family of dogs and that consanguinity was a major feature suggest that common influences affected these dogs. Abnormal cardiac development in this family was manifested in 3 major ways.

1) Anomalies of the Ductus Arteriosus—In the dogs with large PDA, secondary changes in the heart and great vessels were observed. The direction of blood flow through the duct was from aorta to pulmonary artery in each case. Pulmonary hypertension, which may cause shunt reversal, was not detected. The coincidental presence of ductus diverticulum in the other dogs may represent an atypical or incomplete form of hereditary PDA, as found in Poodles.1,2
2) Anomalies of the Tricuspid and Mitral Valves—Congenital tricuspid valve insufficiency has been reported in dog and man, but is considered to be rare.6

In the dog, the tricuspid valve consists basically of 2 valve leaflets, although subsidiary leaflets may be found at each end of the septal flap. The free edges of the leaflets are bound to the ventricular wall by chordae tendineae, which arise from 3 to 4 papillary muscles. Alterations such as short thick leaflets, short or long chordae tendineae, upward malposition of one or more papillary muscles, insertion of a papillary muscle directly onto a valve leaflet, and displacement of the valve downward into the right ventricle (Ebstein's anomaly) have been reported.6 Congenital malformation of the mitral valve, which results in mitral regurgitation, has been reported in other breeds.7,8 Alterations found in the mitral valve of other breeds were similar to lesions discovered in the mitral and tricuspid valve attachments of dog 2, including upward malposition of hypertrophic papillary muscles and of papillary muscles attached directly onto one or both valve leaflets.

In studies with hereditary conotruncal septal defects in the Keeshond,9 a spectrum of malformations ranging from subclinical defects to end-stage tetralogy of Fallot was discovered. Various anomalies along this spectrum included absence of the papillary muscle of the conus (medial papillary muscle) and tricuspid valve anomalies. In nearly all dogs with conotruncal septal defects, the chordae tendineae of the tricuspid valve, which normally insert on the papillary muscle of the conus, were absent or anomalous. Additionally, some dogs had more extensive, hemodynamically significant malformations of the tricuspid valve, such as thickened tricuspid valve cusps bound down by short, thick chordae tendineae. In dog 2, right-side heart failure appears to have developed primarily from tricuspid regurgitation, though PS and PDA certainly contributed. The insertion of a papillary muscle directly into both main leaflets put great restraint on the anterior tricuspid leaflet and probably prevented apposition of the cusps.

Although the pathogenesis of malformations in Salukis and Keeshonden appears different, the involvement of the tricuspid valve suggests some similarity in type of anomalies formed.

3) Anomalies of the Pulmonic Valve—This defect took the form of cusp thickening, with minor fusion in the 1 dog examined at necropsy. In 1 case, it was not possible to demonstrate pulmonic valvular gradients, though valvular thickening could be demonstrated angiographically. Subvalvular or infundibular PS could not be demonstrated in any of the dogs.

In dogs that have PS as a major anomaly, marked ECG and radiographic changes reflect right ventricular enlargement. In the 2 Salukis that had evidence of pulmonic valve involvement and ductus diverticulum, none of the expected enlargement changes was detected. This may have been, at least in part, because the severity of valve involvement was mild and the amount of right ventricular changes was no sufficient to cause an alteration in the ECG or cardiac silhouette. Consideration also must be given to high end-diastolic pressures in the aorta and left ventricle of each of the dogs. Persistence of high pressure in the aorta or left ventricle can result in hypertrrophy, which in these cases was suspected because of ECG patterns of biventricular hypertrophy (dog 3) and left ventricular hypertrophy (dog 4).

The pulmonic valve anomalies did not appear to alter cardiac function. They may, however, be important in understanding the genesis of the cardiac murmurs heard in the other Salukis.

Genetic Considerations—Like all developing systems, the embryonic heart is subject to much variation. This variation may originate in the maternal environment or in the developing embryo's genome. Disease in the dams of the litters or faulty management practices of the pregnant bitch that might influence the health of the offspring could not be identified, though 1 bitch was vaccinated with a modified life-virus vaccine after breeding. Evidence concerning the importance of genetic factors is somewhat more conclusive.

When considering the genetic basis of cardiac disease, 3 modes of inheritance may be considered (1) single mutant gene (mendelian law), (2) chromosome aberration, and (3) polygenic causation.12,13 Although certain diseases in dogs have been shown to be transmitted by various forms of mendelian inheritance, the prevalence is low and there are no data to indicate that these heritable patterns have been established in dogs with congenital heart disease. Similarly, chromosome aberration has not been identified as a cause of major forms of congenital cardiac disease in dogs, though unusual cases have been reported in combination with anomalies of other body systems.13 Chromosome analysis was performed on 2 affected dogs of the group, with negative results. While those results did not provide evidence that chromosome abnormalities did not exist in this group of dogs, it reduced the probability that it was a major factor.

The 3rd mode of inheritance, polygenic inheritance, differs from mendelian inheritance in several important ways. The risk to 1st-degree relatives (siblings and children) is usually 2%–5%, less than the risk of mendelian traits but significantly above that of the general population.14 The risk to 1st-degree relatives is increased if the index case is severely affected or if several in the family are affected, and the prevalence of congenital heart disease is higher in relatives of an index case than in the general population.15 In these dogs, the prevalence in 1st-degree relatives is greater than that in the general population. Communications from Saluki breeders and veterinarians indicate a high prevalence of PS in the breed population. One previous report conducted on dogs with PDA included 2 female Salukis.

Specific hereditary transmission has been demonstrated for FDA in Poodles, pulmonic valvular stenosis in Beagles, fibrous subaortic stenosis in Newfoundland, persistent right aortic arch in German Shepherd Dogs, and tetralogy of Fallot in Keeshonden. Breeding experiments have shown that these defects are not inherited as simple mendelian traits, but that the basis for their disease is polygenic.\(^1\)\(^2\) Although this mode of inheritance appears to be applicable to these cases in the Saluki, positive conclusions cannot be made until controlled mating of affected animals rules out simple mendelian inheritance patterns. A fully penetrant autosomal dominant mode of inheritance is unlikely because, in most cases, 50% of the offspring are not affected and neither the sire nor dam of affected litter has been shown to be affected. However, some animals may have ductus diverticulum as an unetectable lesion, except by angiography. Fully penetrant autosomal or X-linked recessive inheritance may be excluded by mating 2 affected individuals who produce some offspring with anatomically normal cardiovascular systems. Further investigatory breeding experiments must yet be conducted to determine the mode of inheritance.

References