Evaluation of the genetic basis of tricuspid valve dysplasia in Labrador Retrievers

Thomas R. Famula, PhD; Lori M. Siemens, DVM; Autumn P. Davidson, DVM; Martin Packard, PhD

Objective—To quantify inheritance of tricuspid valve dysplasia (TVD) in a population of Labrador Retrievers and evaluate the possibility of the effect of a major locus on TVD.

Animals—521 Labrador Retrievers (345 with known phenotypes and 176 related dogs with unknown phenotypes).

Procedures—Dogs were considered normal, equivocal, and affected for TVD on the basis of echocardiographic appearance of the tricuspid valves. Information on related dogs was collected for estimation of heritability of the 3 categories of phenotype, using a threshold model. Complex segregation analysis was performed to evaluate the possibility of the effect of a major locus on TVD.

Results—Heritability of TVD in this population of dogs was found to be 0.71, a value sufficiently large to suggest a segregating major locus. Subsequent complex segregation analysis did not provide sufficiently strong evidence to indicate influence of a major locus on the prevalence of TVD. However, complex segregation analysis for 2 categories of phenotype (eg, equivocal dogs were grouped with affected dogs) suggested that there was a single recessive allele with a substantial impact on the expression of TVD.

Conclusions and Clinical Relevance—In Labrador Retrievers, TVD is a heritable disorder. Affected dogs and dogs closely related to affected dogs should not be used for breeding. There was insufficient evidence to suggest the influence of a major locus on TVD, although this conclusion was affected by the classification of dogs for diagnosis of the condition.


The proliferation of genetic tests for use in dogs has led to genuine and lasting improvement of companion animals. Von Willebrand's disease, progressive retinal atrophy, and leukocyte adhesion deficiency are among a growing list of disorders in which dogs that are carriers of deleterious alleles can be identified by use of direct genetic tests. These are diseases influenced by a single locus, a situation in which the phenotype of the animal (affected vs normal) can provide a clear view of its genotype. However, many other disorders are the result of expression of numerous genes in combination with environmental factors (eg, hip dysplasia).

The study reported here was conducted to evaluate the inheritance of tricuspid valve dysplasia (TVD) in Labrador Retrievers. Although definitive research on the inheritance of this disorder has not been reported (TVD is considered to be genetically undetermined), evidence suggests this is an inherited condition. Differences in the prevalence of this disorder among breeds of dogs is the first indication of a genetic basis for TVD. There also is evidence that suggests this is an inherited disorder in humans. Quantifying the inheritance of this disorder is required if the intention is to reduce the prevalence of the disease through selective breeding. Quantifying the degree of resemblance among related dogs is achieved through estimation of population heritability.

A congenital heart disease, TVD is characterized by malformation of the tricuspid valve leaflets, chordae tendineae, right ventricular papillary muscles, or a combination of these. The disorder may be evident as an isolated defect or in combination with other congenital diseases such as pulmonic stenosis and mitral valve dysplasia. The malformed tricuspid valve results in variable degrees of regurgitation through the tricuspid valve and, in rare cases, stenosis of the tricuspid valve. Mildly affected dogs generally do not have clinical signs of the disorder. However, dogs with severe TVD usually develop complications early in life such as ascites, pleural effusion, exercise intolerance, syncope, weight loss, and arrhythmias. Development of congestive right-sided heart failure indicates end-stage disease. Medical treatment is directed at controlling or alleviating clinical signs and is merely palliative. For these reasons, selective breeding to avoid the production of affected dogs is the ideal option.

The objective of the study reported here was to quantify inheritance of TVD in a population of Labrador Retrievers, a breed with a high rate of congenital malformation of the tricuspid valve. Genetic progress through selection is best for traits with moderate to high heritability. Accordingly, estimation of heritability will provide breeders with information on the likely success of a breeding program to reduce the prevalence of TVD. Should the estimated heritability suggest that selection against TVD can be accomplished efficiently, we intended to determine whether there was a single locus with a large effect on TVD expression. Most traits, including diseases, temperament, or structural disorders, are the result of many genes as well as environmental influences. However, despite the fact that many genes affect expression, it is often the case that a single locus may have a profound effect on a trait. Such genes, labeled major genes,
can be the focus of additional research. It is plausible that a genetic test could be developed for a major gene. The study reported also included the use of complex segregation analysis to search for any such major locus.12

Materials and Methods

Pedigree analysis—Privately owned Labrador Retrievers that were >4 months old were screened for TVD by use of auscultation and echocardiography. Evaluations were conducted by 17 evaluators; all evaluators were board-certified in veterinary cardiology, radiology, or internal medicine.

Initially, each dog was auscultated, and it was recorded whether a heart murmur was detected. Subsequently, an echocardiogram was obtained for all dogs, even those without murmurs. The tricuspid valve was evaluated by use of 2-dimensional echocardiography, and the amount of regurgitation through the tricuspid valve was assessed by use of color-flow Doppler ultrasonography. Criteria used to establish a diagnosis of TVD included evidence of clubbed, elongated, or thickened valve leaflets; short, thick chordae tendineae or direct attachment of the valve leaflet to the right ventricular papillary muscle; abnormal anatomy of the papillary muscle; dilatation of the right side of the heart; dilatation secondary to regurgitation through the tricuspid valve; or a combination of these findings. The dogs were classified as normal, equivocal, or affected with TVD. The equivocal cat-

Evaluations were conducted with and without correction for ascertainment bias. Using an inappropriate correction for ascertainment bias can be as damaging to the interpretation of results as ignoring ascertainment bias.17 For this reason, complex segregation analysis was conducted with and without correction for ascertainment bias.16 Estimation of heritability is unaffected by an ascertainment bias in progeny, provided the dogs in the base population (ie, dogs without an identified sire or dam) can be regarded as a random sample of the entire population.14

Statistical analysis—To establish and quantify the inheritance of TVD, we estimated the heritability of this ordered categoric phenotype (eg, affected vs equivocal and unaffected dogs). We used threshold models of disease inheritance, intending to estimate the heritability of TVD on a continuous, underlying, and unobservable scale.18 We considered the observation TVD yijk (in which yijk was 0 for affected dogs, 1 for equivocal dogs, and 2 for normal dogs) for the specific dog k (k = 1 to 345) of sex i (i was 1 for males and 2 for females) of guide-dog status class j (j was 1 for guide dogs and 2 for nonguide dogs). The term for guide-dog status was included to evaluate the possibility that the prevalence of TVD may have differed between a population of dogs that was under more intensive scrutiny for breeding selection (eg, guide dogs), compared with that of the general population of Labrador Retrievers.

The assumption of threshold models is such that this categoric phenotype was assumed to be related to an underlying, unobservable, and continuous variate (ie, θ) through a set of 4 fixed thresholds (τ0 = −∞; τ1 = 0; τ2 < τ3; τ3 = ∞). As θ increased in value (attributable to a combination of genetic and environmental contributions, similar to any other continuous, normally distributed trait) and crossed the threshold τ1, the phenotype we observed changed from affected to equivocal. Notice that τ1 was set to a value of 0 for computational convenience without a loss in generality or impact on subsequent data analysis. Accordingly, only τ2 had to be estimated from the data.

The model for θ was similar to any we might have used for continuous phenotypes. The algebraic form of the model was as follows:

\[ θ_{ijk} = \mu + \text{sex}_i + \text{guide}_j + a_k + e_{ijk} \]

where θijk is an unobservable continuous variate for the specific dog k of sex i and guide-dog status j; μ is an unknown constant; sexi is the contribution of the ith sex to TVD expression; guidej is the contribution of guide-dog status to TVD expression; a_k is the additive genetic contribution of the kth dog; and e_{ijk} is an unknown residual. Both a_k and e_{ijk} were assumed to be random effects with a mean of 0 for computational convenience without a loss in generality or impact on subsequent data analysis. Accordingly, only τ2 had to be estimated from the data.

Preliminary analyses also included a term for evaluator; how-

Research in genetic diseases of dogs typically is constructed around affected dogs, called probands. Such data sets provide a biased sample of the population (ie, ascertainment bias).15,36 Failure to accommodate this bias can lead to misinterpreta-

tion of inheritance of the disorder. Methods to correct for ascertainment bias assume that families without affected dogs have not been sampled. Accordingly, the sample in the study reported here appears to be somewhere between a random sample of the population and a proband-centered analysis.
ever, most evaluators had only a limited number of observations in the set of data, and inclusion of this term did not reveal significance. Therefore, this term was deleted from subsequent analyses.

We used a Bayesian strategy to arrive at estimates of $\sigma^2_2$, $\tau^2$, effects attributable to sex and guide-dog status, and the unknown threshold ($\tau$). An advantage of Bayesian methods is the ability to arrive at a point estimate of the unknown variables (eg, heritability) as well as a distributional estimate. Estimation of the distribution of the unknown variables used a technique of numeric integration referred to as Gibbs sampling. The algorithm was based on the iterative generation of a sequence of random variables from the known conditional distributions of the variables, given the likelihood function of the data. Subsequent estimates of the variables were found in the analysis of this sequence of random numbers, called the Gibbs sample. In the study reported here, we generated 250,000 samples of possible heritability. Our estimate of heritability was obtained from the mean of every 25th iterate (after discarding the first 20,000 samples), resulting in a total of 9,200 sample observations (ie, $[250,000 - 20,000]/25 = 9,200$). Variance components were estimated through this Bayesian process by use of a public-domain computer program.

To evaluate the possible segregation of a single locus with a large effect on TVD phenotype, we used regressive logistic models developed for complex segregation analysis. The technique was intended to integrate Mendelian transmission genetics, allele frequency, and penetrance with the patterns of covariance among related dogs expected in polygenic models of inheritance. Several criteria had to be met before acceptance of the major gene model; these criteria were intended to reduce the number of false-positive results. Fitting of the various models necessary for complex segregation analysis of a binary trait was conducted by use of a commercially available software.

For all analyses, results were considered significant at values of $P < 0.05$.

**Results**

Of the 345 dogs (133 males, 212 females) with known phenotypes, 35 (10.14%) were classified as affected with TVD. Of these 35 dogs, 17 were males (12.78% of all males), and 18 were females (8.49% of all females), suggesting that there may be little difference in the prevalence of this disorder on the basis of sex. Among dogs classified as equivocal, 37 were females (17.45% of all females), and 20 were males (13.04% of all males).

Results from the analysis of the threshold model, including an estimate of the heritability of TVD on the underlying, unobservable scale, were summarized (Table 1). The mean heritability of the Gibbs sample was 0.71, with 95% of the values ranging from 0.60 to 0.82. Thus, the disorder clearly appeared to be influenced by mechanisms passed from parent to offspring and is of sufficient magnitude that selection against the disease should be successful. In fact, heritability of this order suggests the segregation of a single locus of large effect. Major loci tend to increase the heritability of a trait in a given population, and a value of 0.71 is comparatively large for polygenic traits.

Equality in the prevalence of TVD between sexes and on the basis of guide-dog status was evident (Table 1). On the underlying scale, the mean difference between sexes was estimated as $-0.21$, with an empirical 95% confidence interval of $-0.71$ to 0.27. An inter-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic variance</td>
<td>2.61</td>
<td>0.84</td>
<td>1.49</td>
<td>4.61</td>
</tr>
<tr>
<td>Heritability</td>
<td>0.71</td>
<td>0.06</td>
<td>0.60</td>
<td>0.82</td>
</tr>
<tr>
<td>Threshold ($\tau$)</td>
<td>1.22</td>
<td>0.19</td>
<td>0.89</td>
<td>1.65</td>
</tr>
<tr>
<td>Sex</td>
<td>$-0.21$</td>
<td>0.25</td>
<td>$-0.71$</td>
<td>0.27</td>
</tr>
<tr>
<td>Guide-dog status</td>
<td>0.07</td>
<td>0.45</td>
<td>$-0.82$</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Estimates were obtained from analysis of a Gibbs sample of 9,200 values. *Dogs were classified as guide dogs or nonguide dogs. CI = Confidence interval.

Results of the complex segregation analysis when TVD was evaluated as a trait with 3 categories in an analysis without ascertainment correction were summarized (Table 2). First, it was evident that the general major locus model (with Mendelian transmission of the putative alleles) did not provide a significantly ($P = 0.30$) better fit than the model in which there was not a major locus, with a likelihood ratio test statistic of 3.66 with 3 degrees of freedom. Accordingly, these results did not provide statistical support for the argument that a single allele with a large effect on TVD was segregating this population of Labrador Retrievers. The analysis conducted with ascertainment correction provided results with similar conclusions and also failed to support a model of a major locus (data not shown).

Interestingly, an alternative conclusion for complex segregation analysis without ascertainment correction was provided, although it was an analysis based on another interpretation of the scored TVD phenotypes (Table 3). In that analysis of the TVD data, dogs that had been classified as equivocal were considered as affected, changing the phenotype analysis with 3 categories to an analysis with 2 categories. Results should be evaluated skeptically, but this analysis may provide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lack of a major locus</th>
<th>General major locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>SE</td>
<td>Estimate</td>
</tr>
<tr>
<td>$P(A)^*$</td>
<td>NA</td>
<td>---</td>
</tr>
<tr>
<td>Pooled base</td>
<td>0.67</td>
<td>0.20</td>
</tr>
<tr>
<td>AA base</td>
<td>NA</td>
<td>---</td>
</tr>
<tr>
<td>AB base</td>
<td>NA</td>
<td>---</td>
</tr>
<tr>
<td>BB base</td>
<td>NA</td>
<td>---</td>
</tr>
<tr>
<td>Parent regression</td>
<td>0.25</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Frequency of the putative major allele A. $^1$Regression effect for parents. NA = Not applicable. --- = Not determined. Natural logarithm of the likelihood for lack of a major locus or a general major locus was $-190.60$ and $-188.77$, respectively.

Table 1—Estimate of variables in a threshold model for tricuspid valve dysplasia (TVD)

Table 2—Estimates and SE obtained from the logistic regression model used in complex segregation analysis of TVD as a phenotype with 3 categories (ie, affected, equivocal, normal) without ascertainment correction
was not significantly \( P \) different from the model for a major locus without a major locus, with a likelihood ratio test statistic of 8.64 with 3 degrees of freedom.

Mendelian transmission of the putative alleles provided a significantly \( P = 0.034 \) better fit than the model without a major locus, with a likelihood ratio test statistic of 2.45 with 2 degrees of freedom. Similar to results for the alternative grouping considered previously, reevaluation of the data with this alternative grouping was conducted in an effort to understand the role of the diagnostic classification and its influence on the inheritance of this disorder. Considered together, the results of the analyses for 3 categories of phenotype and both analyses for 3 categories of phenotype revealed that the genetic nature of TVD diagnosis and the criteria used for determining the progress that can be made in reducing the prevalence of this disease through selective breeding is of critical importance. But for dog breeders, the estimate of heritability (0.71) suggests that selection against parents with known TVD progeny and against the otherwise healthy littermates of affected dogs could considerably reduce the prevalence of this disease.

The results are less clear for the future establishment of a genetic test for TVD. Livestock breeders have been able to generate substantial genetic improvement through the use of large sets of phenotypic data, including the use of pedigree information in large paternal half-sibling families. In such cases, the use of genetic tests has a less obvious advantage. But for dog breeders, a large system for data collection has not been used to compute breeding values and other breeding-selection aids, making the derivation of simple DNA-based tests more attractive. One of the goals of complex segregation analysis is to suggest the potential for success in finding those loci responsible for the expression of disease on which genetic tests can be developed. However, results of the analysis for a trait with 3 categories offered little support for a search of a gene responsible for TVD.

### Table 3—Estimates and SE obtained from the logistic regression model used in complex segregation analysis of TVD as a phenotype with 2 categories (ie, equivocal dogs were classified as affected dogs) without ascertainment correction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lack of a major locus</th>
<th>General major locus</th>
<th>Recessive major locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P(A) )*</td>
<td>NA</td>
<td>0.45</td>
<td>0.42</td>
</tr>
<tr>
<td>Pooled base</td>
<td>0.72</td>
<td>0.17</td>
<td>0.54</td>
</tr>
<tr>
<td>AA base</td>
<td>NA</td>
<td>–5.70</td>
<td>–9.31</td>
</tr>
<tr>
<td>AB base</td>
<td>NA</td>
<td>–1.16</td>
<td>1.75</td>
</tr>
<tr>
<td>BB base</td>
<td>NA</td>
<td>0.74</td>
<td>1.75</td>
</tr>
<tr>
<td>Parent regression†</td>
<td>0.19</td>
<td>0.25</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*See Table 2 for key.

Natural logarithm of the likelihood for lack of a major locus, a general major locus, or a recessive major locus was –113.62, –109.03, and –109.03, respectively.

### Table 4—Estimates and SE obtained from the logistic regression model used in complex segregation analysis of TVD as a phenotype with 2 categories (ie, equivocal dogs were classified as normal dogs) without ascertainment correction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lack of a major locus</th>
<th>General major locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P(A) )*</td>
<td>NA</td>
<td>0.66</td>
</tr>
<tr>
<td>Pooled base</td>
<td>1.36</td>
<td>0.20</td>
</tr>
<tr>
<td>AA base</td>
<td>NA</td>
<td>1.67</td>
</tr>
<tr>
<td>AB base</td>
<td>NA</td>
<td>33.43</td>
</tr>
<tr>
<td>BB base</td>
<td>NA</td>
<td>–54.66</td>
</tr>
<tr>
<td>Parent regression†</td>
<td>0.25</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*See Table 2 for key.

Natural logarithm of the likelihood for lack of a major locus or a general major locus was –88.70 and –86.87, respectively.
Measured as a trait with 3 categories, TVD does not appear to behave as a disease influenced by a single locus of large effect (Table 2). However, when dogs classified as equivocal were reclassified as affected dogs, a recessive major locus would provide a meaningful explanation of the patterns of TVD inheritance in this population of Labrador Retrievers (Table 3). Of course, grouping dogs in this manner may not be medically appropriate. The opposite grouping (ie, dogs classified as equivocal were reclassified as normal dogs) led to the conclusion that a major locus was not part of the expression of TVD (Table 4). The purpose of the reclassification was purely to determine whether the classification of disease influenced our interpretation of the data, which it apparently did. Such a result tells us more about the diagnosis of the disease rather than the inheritance of the disorder. Clearly, TVD is inherited, and the high heritability value is ample justification for this conclusion. However, the scale of observation (mediated through an echocardiogram) did not provide sufficient clarity of diagnosis to permit detection of the contribution of a single locus. For this reason, the search for a major locus, and hence a DNA-based genetic test, should not be attempted until such time that the diagnosis of this disease in affected dogs can be better elucidated. Trying to locate a gene by use of the current classification into 3 categories raises the likelihood that the search for genetic markers would be unsuccessful.

References

Atrial septal defect in five dogs

The clinical, electrocardiographic, radiographic, and two-dimensional, M-mode and Doppler echocardiographic findings of five cases of canine ostium secundum type atrial septal defect (ASD) are described. The atrial septal anomaly was associated with other congenital cardiac abnormalities in two dogs: ventricular septal defect in one case and tricuspid dysplasia in the other. ASD was found in addition to dilated cardiomyopathy and suspected atrial thrombosis in one geriatric dog, but was the only cardiac abnormality detected in the remaining two dogs. Colour Doppler imaging facilitated the diagnosis of ASD in all subjects. The long-term prognosis for dogs with isolated and small-sized ASD is usually good, but can be compromised by the presence of concurrent congenital or acquired cardiac diseases.
subjectively apparent. The other 2D and M-mode echocardiographic parameters measured were within the normal ranges reported in the literature (Bonagura and others 1985, Rishniw and Erb 2000). Doppler echocardiography, spectral and colour-coded, showed a left-to-right systolic-diastolic jet between the atria.

The final diagnosis was ostium secundum type ASD associated with mild right-sided cardiac enlargement. No therapy was prescribed and, at the time of writing, the dog was still alive without further manifestations of cardiac impairment four years after diagnosis.

Case 2
A two-year-old female boxer, of 23 kg bodyweight, was presented with a six-month history of mild exercise intolerance associated with hyperpnoea. No abnormalities were detected on physical examination with the exception of a soft systolic murmur (grade II/VI) localised at the left heart base. Sinus rhythm with a right bundle branch block was present on electrocardiography. Thoracic radiography showed mild cardiac enlargement (VHS, 11:1). A bulging of the cardiac silhouette at the 10 o’clock position was evident on the ventrodorsal view, suggesting right atrial enlargement.

Echo ‘dropout’ in the region of the fossa ovalis, a moderately dilated right atrium and mildly dilated right ventricle were evident on 2D echocardiography. In addition, a mildly dilated left atrium (LA:aorta ratio, 1:7; normal value <1.59, Rishniw and Erb 2000). A left-to-right systolic-diastolic blood flow across the midportion of the atrial septum was observed using colour Doppler imaging (Fig 1).

Ostium secundum type ASD associated with moderate right cardiac chamber enlargement and mild left atrial dilation was diagnosed. No therapy was prescribed and, at the time of writing, the dog was still alive without worsening of the clinical signs three years after diagnosis.

Case 3
An 11-year-old male entire mixed-breed dog, of 24 kg bodyweight, was referred because of dyspnoea, weakness and ascites. Abdominal distension, pulse deficit, irregular heart sounds and a grade IV/VI systolic heart murmur, most audible over the left cardiac apex, were appreciable on physical examination. Respiratory crackles were also detectable on thoracic auscultation. The ECG showed atrial fibrillation (AF) with a ventricular rate of 200 complexes per minute. Global cardiomegaly (VHS, 11:8), associated with enlargement of both arterial and venous pulmonary vessels, and a pulmonary interstitial pattern were evident on survey thoracic radiography.

An ASD in the region of the fossa ovalis, biatrial and biventricular dilation...
associated with reduced left ventricular contractility, slightly thickened mitral valve leaflets, and an echogenic rounded mass in the right atrium, interpreted as a cardiac thrombus, were found using 2D echocardiography (Fig 2). The principal M-mode echocardiographic measurements, compared to normal values reported by Bonagura and others (1985), were as follows: left ventricular diameter at diastole, 58.5 mm (normal range 41.9 to 47.7 mm); left ventricular diameter at systole, 48.6 mm (normal range 28.5 to 33.5 mm); fractional shortening, 17 per cent. The LA and the LA:aorta ratio, measured using 2D echocardiography and compared to normal values observed by Rishniw and Erb (2000), were: LA, 57 mm (normal range 22 to 35 mm), LA:aorta ratio, 3 (normal value <1.59). Left-to-right systolodiastolic flow across the atrial septum and a high velocity systolic regurgitant jet in the LA were recorded using Doppler echocardiography.

The final diagnosis was ostium secundum type ASD, dilated cardiomyopathy, and right atrial thrombosis or a mass associated with congestive heart failure. Digoxin (Lanoxin; GlaxoWellcome), 0.01 mg/kg twice daily, enalapril (Enalfor; Merial), 0.5 mg/kg once daily, and frusemide (Lasix; Hoechst), 2 mg/kg twice daily, were prescribed. Partial remission of the clinical signs was observed during the following three months. However, the dog died nine months after diagnosis from refractory congestive heart failure. A postmortem examination was not carried out.

Case 4
A nine-month-old male entire German shepherd dog, of 16 kg bodyweight, was presented because of failure to grow, dyspnoea, particularly evident during exercise, and cyanosis. The dog was thin and a grade IV/V systolic murmur with maximal intensity over the left cardiac base was audible. An increased respiratory rate (30 breaths per minute) and accentuated bronchovesicular sounds were also appreciable. Sinus rhythm associated with right axis deviation (mean electrical axis-QRS = -120°) and deep S waves in leads I, II, III and aVF were present in the ECG. Thoracic radiography showed moderate rightsided cardiac enlargement (VHS, 10.5).

On 2D echocardiography, a small ASD in the midportion of the atrial septum, a muscular apical ventricular septal defect (VSD), right atrial enlargement and right ventricular dilation and hypertrophy were noted. High velocity (peak velocity, 3.05 m/second; pressure gradient, 37 mmHg) systolic turbulent flow was observed on spectral Doppler echocardiography of the pulmonic blood flow associated with a diastolic regurgitant jet (maximal velocity, 2.53 m/second; pressure gradient, 25 mmHg). Left-to-right systolo-diastolic blood flow across the atria and left-to-right systolic blood flow across the ventricles (Fig 3) were noted using colour Doppler imaging.

Ostium secundum type ASD, a muscular VSD, relative pulmonic stenosis and insufficiency associated with suspected pulmonary hypertension were diagnosed. The dog died four days later. A postmortem examination was not carried out.

**Table 1. Summary of clinical, electrocardiographic (ECG) and radiographic findings in five dogs with ostium secundum type atrial septal defect**

<table>
<thead>
<tr>
<th>Case</th>
<th>Signalment</th>
<th>History</th>
<th>Clinical signs</th>
<th>ECG</th>
<th>Thoracic radiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Irish Setter, 3 years old, F</td>
<td>Exercise intolerance, hyperpnoea</td>
<td>Cardiac arrhythmia, soft systolic murmur</td>
<td>Ventricular escape complexes</td>
<td>Right heart enlargement, pulmonary overcirculation</td>
</tr>
<tr>
<td>2</td>
<td>Boxer, 2 years old, F</td>
<td>Exercise intolerance, hyperpnoea</td>
<td>Soft systolic murmur</td>
<td>Right bundle branch block</td>
<td>Right atrial enlargement</td>
</tr>
<tr>
<td>3</td>
<td>Mixed breed, 11 years old, M</td>
<td>Depression, dyspnoea, ascites</td>
<td>Cardiac arrhythmia, systolic murmur, congestive heart failure</td>
<td>Atrial fibrillation</td>
<td>Global cardiomegaly, dilated pulmonary vessels, pulmonary interstitial pattern</td>
</tr>
<tr>
<td>4</td>
<td>Mixed breed, 9 months old, F</td>
<td>Failure to grow, exertional cyanosis, dyspnoea</td>
<td>Poor body condition, systolic murmur</td>
<td>Right axis deviation</td>
<td>Right heart enlargement</td>
</tr>
<tr>
<td>5</td>
<td>German shepherd dog, 18 months old, F</td>
<td>Heart murmur</td>
<td>Poor body condition, systolic murmur</td>
<td>Splintered R wave</td>
<td>Severe right heart enlargement</td>
</tr>
</tbody>
</table>

F Female, M Male
DISCUSSION

The haemodynamic consequence of ostium secundum type ASD is blood flow between the two atria. Since the pressure gradient between the left and the right atrium is very low, the direction of the shunt is mainly related to ventricular compliance. Owing to its thinner wall, the right ventricle has a higher compliance than the left ventricle (Kittleson 1998). Therefore, the blood usually flows in a left-to-right direction (Kittleson 1998), as observed in dogs 1, 2 and 3 in the present report. The expected consequence of intracardiac left-to-right blood shunting is right-sided cardiac overload; the severity depends on the dimension and duration of the septal defect (Boon 1998). Pulmonary overcirculation and left atrial enlargement can occur with large defects, in addition to relative stenosis of the tricuspid and pulmonic valves and/or pulmonary hypertension (Bonagura and Lehmkull 1999). In such cases, the right ventricular compliance diminishes and, as a consequence, reversed (right-to-left) interatrial shunting and, eventually, cyanosis can develop (Eisenmenger’s syndrome).

Other causes of right-to-left trans-atrial blood flow include the presence of concurrent congenital cardiac disease, leading to increased right-sided cardiac pressure (Lombard and others 1989). Cyanosis was evident during physical activity in dog 4 (ASD associated with VSD), and was not observed in dog 5 (ASD associated with tricuspid dysplasia). Suspected pulmonary hypertension, based on a Doppler-derived, pulmonary artery to right ventricle diastolic pressure gradient of 25 mmHg (Johnson and others 1999), and exercise-induced decreased peripheral vascular resistance (Friedman 1997), were likely to be responsible for cyanosis in case 4.

The clinical signs of small-sized ostium secundum type ASD are often vague and non-specific (Kirberger and others 1992, Eyster 1994, Kittleson 1998). Therefore, the true prevalence of the anomaly may be underestimated. The diagnosis can be an incidental finding when performing cardiac catheterisation or echocardiographic examination for concurrent cardiovascular diseases (Buchanan and others 1963, Lombard and others 1989). For the same reason, ASD is one of the most commonly recognised congenital cardiac diseases of adult men but is rarely diagnosed in infants (Friedman 1997). Right-sided congestive heart failure usually occurs only when a large defect is present (Bonagura and others 1999). Exercise intolerance, dyspnoea and a soft systolic murmur over the left heart base, probably secondary to relative pulmonic stenosis, were appreciable in dogs 3, 4 and 5, which were mainly related to concurrent, congenital or acquired, cardiac diseases associated with the ASD.

Deep S waves in leads I, II, III and aVF, right axis deviation of the QRS and delayed ventricular conduction are the main ECG abnormalities described in dogs with ASD (Hamil and others 1963, Tidholm 1997, Bonagura and others 1999). ST segment deviation were present in dog 3, both of which had a large and isolated ASD. The clinical signs of dogs 3, 4 and 5 were mainly related to concurrent, congenital or acquired, cardiac diseases associated with the ASD.

Case 5
A 18-month-old female German shepherd dog, of 26 kg bodyweight, was referred for the re-evaluation of an ASD associated with tricuspid dysplasia diagnosed at the age of six months by a colleague. Thereafter, the dog had received enalapril (Enal- for; Merrell), 0.5 mg once daily, and frusemide (Lasix; Hoechst), 0.5 mg/kg twice daily. The dog was very thin and a grade IV systolic murmur, most audible at the right cardiac apex, was appreciable. Sinus rhythm and a ‘splitter’ R wave were recorded on electrocardiography. Thoracic radiography showed severe right-sided cardiac enlargement (VHS, 12–6).

A large ASD was evident on 2D echocardiography associated with an elongated anterior leaflet and tethered septal leaflet of the tricuspid valve. An extremely dilated right atrium and right ventricle, paradoxical ventricular septal motion and reduced left ventricular dimensions were also evident. A wide systolic regurgitant jet across the tricuspid valve was noted on colour Doppler imaging (Fig 4). Blood flow across the ASD had a left-to-right direction during systole (Fig 5A) and right-to-left direction during systole (Fig 5B) as a consequence of increased systolic right atrial pressure secondary to tricuspid regurgitation.

The diagnosis of ostium secundum type ASD associated with tricuspid dysplasia was confirmed and the previous therapeutic protocol was maintained. At the time of writing, the dog’s condition was stable, one year after referral.

The clinical, electrocardiographic and radiographic findings observed in all dogs are summarised in Table 1, and the echocardiographic and echo-Doppler findings are summarised in Table 2.

### Table 2. Two-dimensional (2D), M-mode and Doppler echocardiographic findings, and final diagnosis in five dogs with ostium secundum type atrial septal defect (ASD)

<table>
<thead>
<tr>
<th>Case</th>
<th>2D and M-mode echocardiography</th>
<th>Doppler echocardiography</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ostium secundum type ASD, dilated right atrium and ventricle</td>
<td>Systolo-diastolic jet between LA and RA</td>
<td>Ostium secundum type ASD</td>
</tr>
<tr>
<td>2</td>
<td>Ostium secundum type ASD, dilated right atrium and ventricle, increased LA: Ao ratio</td>
<td>Systolo-diastolic jet between LA and RA</td>
<td>Ostium secundum type ASD</td>
</tr>
<tr>
<td>3</td>
<td>Ostium secundum type ASD, dilated cardiac chambers, reduced FS, rounded mass in right atrium</td>
<td>Systolo-diastolic jet between LA and RA, systolic regurgitant jet across mitral valve</td>
<td>Ostium secundum type ASD, dilated cardiomyopathy, suspected atrial thrombosis</td>
</tr>
<tr>
<td>4</td>
<td>Ostium secundum type ASD, ventricular septal defect, right atrial enlargement, right ventricular dilation and hypertrophy</td>
<td>Systolo-diastolic jet between LA and RA, interventricular flow, high velocity systolo-diastolic flow across pulmonic valve</td>
<td>Ostium secundum type ASD, ventricular septal defect, relative pulmonic stenosis, suspected pulmonary hypertension</td>
</tr>
<tr>
<td>5</td>
<td>Ostium secundum type ASD, abnormal tricuspid valve leaflets, severely dilated right atrium and ventricle</td>
<td>Bidirectional jet between LA and RA, systolic regurgitant jet across tricuspid valve</td>
<td>Ostium secundum type ASD, tricuspid dysplasia</td>
</tr>
</tbody>
</table>

*Normal echocardiographic values used for comparison are derived from Bonagura and others (1985, Herbage (1994) and Rishniw and others (2000)
Atrial septal defect in 5 dogs  27/2/03  15:27  Page 321

The present authors used colour Doppler imaging to confirm the presence of ASD in all subjects. The same technique was employed in dog 4 to diagnose muscular apical VSD, which represents an uncommon location for a ventricular septal abnormality (Boon 1998, Bonagura and Lehmkhu 1999). In fact, VSD usually involves the perimembranous portion of the ventricular septum, just proximal to the aortic valve and just beneath the septal leaflet of the tricuspid valve (Kaplan 1991, Eyster 1994, Kittleson 1998). The combined use of spectral Doppler and colour Doppler imaging was applied to diagnose other blood flow abnormalities associated with ASD: mitral regurgitation in dog 3, relative pulmonic stenosis and insufficiency in dog 4, and tricuspid regurgitation in dog 5.

The lack of postmortem confirmation of the observed defect was a limitation of the present study. Furthermore, neither cardiac catheterisation nor angiography were employed to confirm the diagnosis. Nevertheless, the authors consider that the combined use of 2D and Doppler echocardiography provided convincing evidence.
of the presence of ASD in all cases, as has already been demonstrated in human patients (Friedman 1997).

The long-term physical condition of the two dogs with isolated and small-sized ASD (cases 1 and 2) was good without treatment. Frusamide and enalapril were employed to reduce venous congestion and afterload in dog 3, in addition to digoxin administration which aimed to slow the ventricular rate in the presence of AF. Cardiac impairment in this dog was mostly attributable to dilated cardiomyopathy, in addition to long-standing ASD. Concurrent atrial and ventricular septal defects associated with suspected pulmonary hypertension were responsible for the severity of heart disease in dog 4. A diuretic and ACE inhibitor were used to reduce systemic vascular resistance and bidirectional shunt in dog 5 (Gardon and Amberger 1998, Kittleson 1998). The physical condition of this subject was relatively good in spite of concurrent large-sized ASD and severe tricuspid dysplasia.

Surgical repair of canine ASD has rarely been attempted (Eyster and others 1976, Jeraj and others 1980, Eyster 1994, Nakayama and others 1994, M onnet and others 1997). Dogs with small-sized ASD do not need surgical intervention. Surgery is costly and usually requires cardiopulmonary bypass or other techniques to arrest the heart (Bonagura and Lehmkuhl 1999). Furthermore, the long-term prognosis for surgical patients is usually poor (Jeraj and others 1980, Nakayama and others 1994, Kittleson 1998). A percutaneous technique using different transcatheter occluders under fluoroscopic or transesophageal echocardiographic imaging guidance is often used for closure of ASD in humans (Friedman 1997). To the best the authors’ knowledge, the use of this technique has not been described in the veterinary literature.

Conclusions

Ostium secundum type ASD is a rare canine congenital cardiovascular disease characterised by vague and usually non-specific clinical signs when concurrent cardiovascular diseases are absent. Electrocardiographic and survey thoracic radiographic findings can also be non-specific in affected animals. Echocardiography is a useful tool for the diagnosis of ASD, but care must be taken when examining the thin atrial septal wall in the region of the fossa ovalis due to the echo ‘dropout’ that can also be observed in healthy animals. Colour flow Doppler echocardiography offers a non-invasive way of confirming the presence of the anomaly without the need for cardiac catheterisation or angiography. Medical or surgical management of small uncomplicated defects is usually not necessary.

References


Dogs with the largest PDA (grade 6) may develop a right-to-left shunting over time. In this type of ductus there is a matching resistance on both sides of the circulation, blood pressures equalizes in the aorta and the pulmonary artery as a result of the increase in pulmonary blood flow leading to pulmonary hypertension. The increase in pulmonary blood flow creates pathologic responses in the pulmonary arteries over time. The exact mechanism for this process is unknown but probably involves injury to the endothelial cells that activates growth factors (4). These factors induce smooth muscle cell hypertrophy and hyperplasia and promote connective tissue protein synthesis. The pathologic response consists primarily of medial hypertrophy and intimal proliferation in the medium and small pulmonary arteries. When the right-to-left shunt is clinically significant a large amount of deoxygenated blood shunts into the aorta beyond the region where the ductus joins the aorta. Caudal body arterial oxygen tension is commonly between 30-45mmHg leading to a weakness of the hindlimbs, mainly during exercise, and polycythemia due to the low oxygenation of the renal tissue that will subsequent release erythropoietin.

DIAGNOSIS

Many dogs with lef-to-right shunting show only a continuous cardiac murmur detected mainly during the routine visit or vaccinations. The murmur is best heard over the left axillary area that irradiates to the right side. A separate murmur as a result of mitral regurgitation may be auscultated over the left apex and is due to mitral annular dilatation. Dogs with moderate-to moderately large shunts that are not diagnosed when the dog is young may present as adults with signs of left heart failure. The femoral pulse is often described as a bounding pulse. Dogs with right-to-left shunting usually present with rear limb collapse upon exercise. The exercise results in a decrease in systemic vascular resistance, whereas pulmonary vascular resistance is fixed because of the pulmonary arterial disease. Consequently, exercise produces an increase in right-to-left shunting resulting an exacerbation of cyanosis and weakness of the rear limbs.

Radiographic changes depend on the size of the PDA. In mild cases, it is possible to observe only the overcirculation pattern characterized by an increased pulmonary vascular size. However the variation in pulmonary vascular size in normal dogs sometimes makes this finding difficult. Dogs with a relatively large left-to-right shunt commonly have an enlargement of the left ventricle, left atrium and a dilated aortic arch, giving the appearance of generalized cardiomegaly. An aneurysmal bulge in the descending aorta in the region of the ductus is a common finding on the dorsoventral or ventrodorsal radiograph. In cases with an increased main pulmonary artery, it may be observed as a bulge at the 2-o’clock position on the dorsoventral or ventrodorsal radiograph. Pulmonary venous enlargement and pulmonary edema may be visible in dogs with left heart failure.
The most common abnormality on the electrocardiogram is an increase in R wave amplitude in lead II as a result in left ventricular enlargement. This finding is present in approximately 50% of cases with left ventricular enlargement (5).

There is a clinical classification made by physical examination, plain radiographs and electrocardiogram that describes 4 types of PDA. Type 1 is a small PDA, type 2 is a medium size PDA, Type 3a is a large PDA prior to congestive heart failure, type 3b is a large PDA plus congestive heart failure and type 4 is a large PDA plus pulmonary hypertension (5a).

The echocardiogram provides direct evidence for the presence of the PDA as well as permits an evaluation of the hemodynamic consequences. In the left-to-right shunting, the left ventricular end-diastolic diameter and left atrium size are increased and generally correspond to the size of the PDA. Left ventricular end-systolic diameter is normal to increased with a shortening fraction usually within the normal range. Color flow and spectral Doppler may reveal the presence of continuous turbulent flow in the main pulmonary artery from the right parasternal short axis view and from the left parasternal cranial view. Spectral Doppler permits one to evaluate the Qp/Qs which gives the information of the shunt fraction. Qp/Qs ≥ 2 means that the dimension of the ductus is from moderate to large. Peak velocity through the ductus, when there is no increased resistance in the pulmonary artery, is between 4 and 6m/sec. Peak aortic velocity is frequently increased due to the volume overload. In our experience, the best echocardiographic projection in order to visualize the ductus in 2-dimensional mode and measure the pulmonary side dimension of the PDA, is the left parasternal cranial view, trying to avoid the bifurcation of the pulmonary artery by making a very mild movement in a craniodorsal direction. From this projection, it is also possible to observe the aneurysmal dilation of the ductus in some cases, but a complete examination of the morphology of the ductus is not possible to do with transthoracic echocardiography. Good alternatives are trans-esophageal echocardiography (TEE) and angiography. TEE can be used to enhance the visualization of the PDA contributing to the understanding of the anatomical structure, as well as allow measurement of the minimal and the maximal diameter of the PDA (6,7). Angiocardiography also gives the knowledge of the ductal morphology and dimensions (8). Dimension and morphology of the PDA are important measurements in order to select the best therapeutical approach. Right to left shunting PDA may be documented with echocardiography as well as angiography. In order to demonstrate the right to left shunting with echocardiography, we can inject (into the cephalic vein) a microbubbles contrast study (saline mixed with dextran solution) while we visualize the abdominal aorta. In the right to left shunt we see the microbubbles in the abdominal aorta which normally should not be seen because of the pulmonary entrapment. If we see microbubbles in the abdominal aorta, it means that the bubbles had to bypass the lungs which means that they had to pass from the pulmonary artery to the aorta through a reversed ductus. Cardiac catheterization may also be used to document the presence of a right-to-left shunting PDA. Injection of radiopaque dye into the right ventricle outlines the right ventricle, the main pulmonary artery, the large PDA and the descending aorta. Simultaneous right and left ventricular pressure measurements demonstrate very similar systolic pressures; simultaneous aortic and pulmonary artery pressure measurements verify equilibration of pressures. In very few cases it is possible to visualize with echocardiography a left to right shunting PDA with a reduction or loss of the diastolic flow and severe high velocity tricuspid regurgitation. In those cases, cardiac catheterization is imperative in order to better evaluate the presence and entity of pulmonary hypertension before any PDA closure.

TREATMENT

Closure of the PDA is always recommended. It may be done by surgical ligation or with a percutaneous device. We close the PDA surgically if the PDA minimal dimension is bigger than 5-6mm, or if the morphology of the ductus is tunnel-like. Several articles have been published in veterinary medicine describing several methods of transarterial ductal occlusion. The most frequent method reported in veterinary medicine is the transcatheter closure of patent ductus arteriosus using Spring Coils (Miller MW 1995, Snaps FR 1995, Fellows CG 1998, Schneider M 1998, Stokhof AA 2000). Some of them describe coil position using detachable coils with a mandril wire that passes into the lumen of the coil as a delivery system, while others reports describe coil position using an uncontrolled release system. Other devices have been described in veterinary medicine: Ronald G. Griffka closed a PDA in a Newfoundland puppy using the Gianturco-Griifka vascular occlusion device that allows the possible closure of PDAs from 3 to 9mm (8a); Philip R. Fox described a technique occluding a PDA in two dogs using a preformed Nitinol snare in order to facilitate coil placement and decrease the pulmonary or aortic embolization (9); Saunders reported a modified technique, using a balloon occlusion catheter at the pulmonary side to facilitate transarterial coil embolization (10); David Scission presented a new technique to occlude bigger PDAs using the Amplatzer duct occluder (11); other methods described in human medicine to occlude big PDAs are the 2 coils crossover technique to occlude big PDAs in dogs using the 2 coils crossover that actually has been completely supplied by the Amplatzer duct occluder. One common point in all these articles is the PDA dimension which is a determining factor in using one or another device, as well as the need for conventional surgery. A recent article evaluates the feasibility and treatment of choice of catheter closure of large and small PDAs in dogs. It shows that coil embolisation is readily feasible for closure of PDA < 4 mm, less feasible for PDA < 5mm and unlikely to be feasible to close PDA > 5mm in which case, the Amplatzer duct occluder is the best device for closure(12). Another point to consider is the morphology of the PDA that has to be evaluated with fluoroscopy.
prior coil embolization. Age of the patient is important in order to maintain left sided cavities within normal values after the procedure. We have observed that young patients tended to reduce left ventricular dimensions within normal values after the procedure, while older patients still maintain increased LV dimensions but observing an improved cardiac function. This finding corresponds with a recent article that describes the effect of the closure of the PDA in older dogs (13). Patient body weight is another factor to consider because patients less than 4Kg are too small to perform this kind of technique, because of the physical and material limitation, as well as the higher risk of complications. As we can see PDA patient selection is very important, so parameters to evaluate are: body weight, age, PDA clinical classification, PDA dimensions and morphology. Traditionally, PDA dimensions are obtained from angiocardiography. We have observed a good correlation between measurements done with echocardiography and those obtained by angiocardiography (no published data). We start doing a PDA dimension selection with transthoracic or transesophageal echocardiography, in order to know using a non-invasive method, the PDA dimensions, and then decide if the patient can be treated with an interventional technique or otherwise require surgery. Transthoracic echocardiography is limited in evaluating PDA morphology which can only be completely evaluated by transesophageal echocardiography or by an invasive method such us angiocardigraphy. Furthermore TEE permits you to assist and monitor the closure of the PDA during the transcatheter coil embolization (14) and we also use TEE for confirmation of a completely surgical closure of the ductus during conventional surgery.

References

DIAGNOSIS AND TREATMENT OF PULMONIC STENOSIS

Oriol Domenech, DVM
Clinica veterinaria gran sasso
Milan, Italy
and Survet Diagonal**
Barcelona, Spain

There are three types of pulmonic stenosis: subvalvular pulmonic stenosis, valvular pulmonic stenosis, and supravalvular pulmonic stenosis. The most common type is the valvular pulmonic stenosis which is the most frequent congenital heart defect in our clinic. Pulmonic stenosis, in contrast to subaortic stenosis, usually presents with a definite grade of severity early in the life of the affected puppy.

A heritable basis for pulmonic stenosis has been proven in beagles and keeshonds, based on breeding studies (1-3). Other breeds at increased risk for pulmonic stenosis include English bulldogs, French bulldog, Boxer, American cocker spaniel and West Highland White Terrier.

In humans, valvar stenosis is further subdivided into dysplastic valve leaflets with anular hypoplasia and no poststenotic dilation, and cases with non-dysplastic valves and fused leaflets (4). In veterinary medicine, a similar criteria of subdivision has been published differentiating PS into 2 main types (5):

- **Type A**: annular size is normal. Various degrees of leaflet thickening with incomplete separation of the commissures to almost complete fusion. It causes a systolic doming of the valve (“windsock” type image) with, most often, eccentric valvular opening and various degrees of reduced cross-sectional area. Poststenotic dilatation of the pulmonary trunk is present with various degrees of severity.

- **Type B**: the pulmonary ostium is hypoplastic, with various degrees of valvular leaflet thickening and immobility, but little commissural fusion. The main pulmonary trunk is also often hypoplastic, and rarely has a poststenotic dilatation.

Subvalvular obstructions by a fibrous ring, analogous to SAS, appear to be rare and are invariably associated with additional valvular deformities. Various degrees of fibromuscular infundibular hypertrophy is the more common form of subvalvular PS; likely, it has a dynamic component and leads to worsening of the stenosis with exercise or during stress tests. In some breeds, especially the English bulldog and Boxers, an anomalous R2A-type left coronary artery encircles and constricts the right ventricular outflow tract. This anomaly represents an exclusion criteria for any valvuloplasty procedure, as a dilation of the infundibulum would lead to severe coronary ischemia and the patient’s demise.

Isolated supravalvular PS appears to be extremely rare. During the echocardiographic examination, attention should be given to the systolic doming of the valve in type A PS cases because supravalvular PS could be easily misdiagnosed.

Combination of SAS and PS occurs in a considerable number of boxers. In one retrospective study of 500 Boxers a combination of the SAS and PS occurred in 24% of dogs with cardiac disease (6).

Obstruction to right ventricular outflow tract (RVOT) causes an increase in right ventricular systolic pressure and wall stress leading to right ventricular hypertrophy, left-ward septal deviation or flattening, and a systolic pressure gradient across the pulmonary valve. With the progression of the disease, a right sided congestive heart failure develops. Progressive right atrial enlargement results from various factors including elevated right ventricular diastolic pressure, secondary tricuspid regurgitation caused by high systolic pressure and geometric changes within the right ventricle, right ventricular hypokinesia (right ventricle loses force of contraction in a similar way as the left ventricle in advanced cases of aortic stenosis) and decreased cardiac output with compensatory retention of sodium and water.

**DIAGNOSIS**

Usually dogs are asymptomatic, showing only a left basilar ejection murmur over the pulmonic valve that radiates to the left craniodorsal cardiac base. It is not uncommon to auscultate a holosystolic murmur of tricuspid regurgitation over the right hemithorax. Some cases present with ascites, exercise intolerance and syncope related to right-sided congestive heart failure and low cardiac output. Sudden death without premonitory signs may occur.

Electrocardiography often shows a pattern of right ventricular enlargement; ventricular arrhythmias and supraventricular arrhythmias may also be present. Thoracic radiographs are usually normal in mild to moderate affected animals but right-sided cardiomegaly may be present. In moderate to severely affected animals with Type A pulmonic stenosis. Poststenotic dilation of the main pulmonary artery may be observed. Pulmonary underperfusion may be observed depending on the severity of the stenosis. Echocardiographic examination is the most important diagnostic tool used to identify the presence of this congenital heart defect as well as permit classification of the different type and severity of PS. The right ventricular outflow tract has to be optimized in its entire length with a perfect long axis view, although this may be difficult in many cases due to its curved course. Initially an oblique, somewhat tangential section of the RVOT, obtained from a right parasternal short axis view, can be generated in all dogs which permits you to approximately measure the pulmonary annulus. Then, this projection may be optimized by moving the probe versus to the sternum, maintaining the same angle section, trying to get the maximum length of the RVOT, pulmonary annulus and mean pulmonary trunk (this last section is the best in order to perform the Doppler recordings obtained with the spectral and color flow Doppler). In patients with subvalvular PS, these views are sufficient to image
subvalvular narrowing caused by muscular hypertrophy as well as to observe the presence of a dynamic stenosis which is not uncommon. Dynamic stenosis is well observed with the spectral Doppler characterized by a “knife-shaped” flow pattern. In some cases of valvular PS, the only visual abnormality is a wide RVOT with a thickened, hypertrophic free RV-wall. The valvular and supravalvular lesions are too proximal to be seen properly in these cases. Despite the lack of visualization, the pulsed wave Doppler and continuous wave Doppler reveal a systolic turbulent jet and maximal outflow velocity respectively. In such cases, left sided views may be attempted in order to complete the echocardiographic examination. A left cranial parasternal short axis view is obtained doing a steep dorsal and slightly more cranial angulation after obtaining a long axis view of the aortic root; this projection allows one to see the RVOT with the main pulmonary artery in most of its length and even the bifurcation into left and right main pulmonary arteries. This view also displays valvular abnormalities and poststenotic dilatations nicely. When elevated peak velocities are found in the RVOT, the values are then transformed into an estimated pressure gradient with the simplified Bernoulli equation, the same way as with SAS. The obtained values are classified as mild, moderate and severe when peak gradient is less than 50 mmHg, from 50 to 80 mmHg and more than 80 mmHg respectively. Pulmonic regurgitation is commonly observed.

Natural history depends on lesion severity. Dogs affected by mild and even moderate PS may live normally. Animals with moderate-to-severe stenosis may develop complications, including exertional syncope, cardiac arrhythmias, secondary tricuspid regurgitation, atrial fibrillation, right congestive heart failure and sudden death. Systolic pressure gradients are not always predictive of clinical outcome but a general correlation can be observed between pressure gradient and survival.

TREATMENT
Medical Treatment
The decision to treat pulmonic stenosis is based on the severity of clinical signs and the magnitude of the pressure gradient across the pulmonic valve. The pressure gradient for which a medical treatment should be recommended cannot be stated with certainty. Usually with a pressure gradient greater than 50-60 mmHg a medical treatment based on a beta-blocking agent could be started. This drug reduces myocardial oxygen demand and increases coronary perfusion by decreasing heart rate and contractility; these effects may help in preventing or at least reducing the incidence of the late stage characterized by right ventricular myocardial insufficiency. Also this drug reduces the dynamic stenosis at the RVOT as it reduces the heart rate and contractility. The reduction of the dynamic stenosis is very important in cases where a pulmonary balloon valvuloplasty will be performed. Atenolol is used as in SAS cases, with a starting dose of 0.2 mg/Kg SID or BID.

Balloon Dilation
Pulmonary balloon valvuloplasty (PVB) was first described by Kan and others as a new method of treating children with congenital pulmonary valve stenosis (7). Five years later the first successful application of balloon dilation in the therapy of pulmonic stenosis in a dog was reported by Bright et al. (8). Since that time, several reports have shown the safety and efficacy of the pulmonary balloon valvuloplasty (Sisson and MacCoy 1988, Thomas and others 1990, Browlie and others 1991, Martin and others 1992, Eric de Madron and others 1995 and Bussadori and others 1998). A brief report by Ewey et al (9) showed the 2 year survival rate was much better in dogs treated by PVB, than untreated dogs or those treated by surgery. Short term studies (10), medium term studies (11, 12) and long term studies (13) also yielded promising results. We have observed that type B pulmonic stenosis has a lower response to the pulmonary valvuloplasty, so valvular anatomy (type A or type B) is an important discriminator of good outcome post-valvuloplasty in dogs with pulmonic stenosis (12, 14). It is alreday well known that anomalous left main coronary artery (originating from a single right coronary artery) (15) wich encircles the stenotic RVOT, is present in some affected dogs, especially in English Bulldogs and Boxers, so coronary anatomy examination with a selective coronariography is strongly recommended.

We have done almost 70 pulmonary valvuloplasties in dogs and the major complications that have been observed are: right ventricle perforation, S-T segment depression, ventricular tachycardia, and ventricular fibrillation, however only one dog died from ventricular fibrillation. Therefore, the complications we have observed during pulmonary valvuloplasty are quite various but have a low incidence of mortality. Right ventricle perforation, with a consequent pericardial effusion and presence of contrast in pericardial space, is the most spectacular complication we have seen but it never resulted in pericardial tamponade nor death. Otherwise S-T segment depression, as a sign of myocardial ischemia, is less apparent but it is very important because the patient is in an elevated risk to develop a severe ventricular tachycardia. Ventricular tachycardia usually responds very well to lidocaine infusion unless there is a severe myocardial ischemia. These complications are related to material, procedure technique, size of patient, patient stability before the procedure, type of the stenosis and experience of the operator. We have also observed that patients pre-treated with beta-blocking agents presented with much less incidence of malignant arrhythmias as well as less worsening of the dynamic pulmonic stenosis. It is not uncommon to observe a worsening of the dynamic pulmonic stenosis after the dilation of the stenosis due to the decreased resistance of the RVOT that results in an exaggerated systolic motion of the infundibular area of the RVOT. This is a very serious problem which may result in the patient’s death. We now pre-treat all patients that will be undergoing a PVB with a beta-blocking agent (atenolol).
We also find errors of the catheterization that may complicate the procedure, the most frequent are: contrast tattoo, air ball, inappropriate localisation of the catheter during contrast injection and guide wire loop formation in the right atrium or right ventricle.

References

La estenosis pulmonar (EP) es el segundo defecto cardíaco congénito más frecuente en el perro, en la mayor parte de los estudios recientes sobre prevalencia de las anomalías congénitas\textsuperscript{1,2}.

Aunque se han descrito las formas subvalvular y supravalvular, la forma más común de obstrucción del tracto de salida del ventrículo derecho (OTSVD) en perros es la displasia valvular\textsuperscript{3}. Puede estar presente como defecto aislado o asociado a otros defectos. Dos tipos principales (y también formas intermedias) han sido descritos: Tipo A: las valvas pulmonares presentan varios grados de engrosamiento con mayor o menor fusión de las comisuras; el anillo valvular es de tamaño normal con varios grados de dilatación posestenótica. Tipo B: las valvas pulmonares aparecen engrosadas e inmóviles con escaso grado de fusión de las comisuras y ostium pulmonar hipoplásico\textsuperscript{3,4}. En perros Bulldog inglés y Boxers la EP puede estar asociada con una arteria coronaria anómala que rodea el tronco pulmonar justo por debajo de la válvula, causando estenosis subvalvular. La forma más extrema de OTSVD lo representa la atresia de la arteria pulmonar.

- **Predisposiciones raciales:** Bulldog inglés, Mastiff, Fox terrier, Samoyedo, Schnauzer miniatura, Cocker Spaniel y West Highland White Terrier están especialmente predispuestos. En perros Beagle se ha descrito una forma hereditaria de estenosis pulmonar (transmisión poligénica)\textsuperscript{4} y también en perros Boykin Spaniel.

- **Fisiopatología:** la OTSVD causa incremento de la resistencia a la eyeción y un incremento proporcional de la presión sistólica ventricular, dando hipertrofia ventricular derecha, septo interventricular desviado hacia el lado izquierdo y un gradiente de presión a través de la válvula pulmonar. El flujo turbulento a través de la válvula pulmonar es responsable de un soplo sistólico con punto de máxima intensidad sobre la base cardíaca izquierda y dilatación posestenotica de la arteria pulmonar. A veces se encuentra asociada insuficiencia tricúspide,
bien por malformación congénita de la misma o secundaria a la hipertrofia de los músculos papilares y exceso de presión en ventrículo derecho.

Evaluación clínica: Los animales con EP leve son habitualmente asintomáticos. Los casos severos muestran signos relacionados con bajo gato cardíaco, tales como intolerancia al ejercicio y síncope y a menudo fallo cardíaco derecho. La auscultación torácica revela un soplo sistólico sobre el foco de la válvula pulmonar que irradia dorsalmente. Si existe regurgitación tricuspídea se ausculata un soplo holosistólico en el hemitórax derecho, sobre el foco tricuspídeo. El electrocardiograma (ECG) es normal en estenosis leves. En las formas moderadas a severas el ECG muestra un desvío del eje eléctrico hacia la derecha en el plano frontal y ondas S profundas en derivaciones precordiales izquierdas. En las radiografías torácicas se observan varios grados de agrandamiento ventricular derecho, arteria pulmonar principal prominente y pulmones hipoperfundidos. Mediante ecocardiografía se puede visualizar la obstrucción. Cuando existe fusión valvular, las cúspides aparecen fusionadas en los bordes de las sigmoides, dando imagen de cúpula. Cuando existe hipoplasia la válvula aparece engrosada e inmóvil y el anillo estrecho e hipoplásmico. Los principales efectos hemodinámicos de la EP moderada a severa se visualizan ecocardiográficamente en forma de hipertrofia ventricular concéntrica, movimiento septal paradoxal y reducido tamaño de atrio y ventrículo izquierdos. La dilatación de la arteria pulmonar principal puede ser vista distalmente a la obstrucción, cerca de la bifurcación. La ecocardiografía Doppler espectral de la EP mostrará un incremento del pico de velocidad del flujo en la arteria pulmonar (> 1.6 m/seg) y a menudo insuficiencia pulmonar. Las EP con un gradiente de presión Doppler (GPD) a través de la estenosis ≤ 50 mm Hg se consideran estenosis leves. Gradientes entre 50 y 80 mm Hg son EP moderadas y gradientes ≥ 80 mm Hg se asocian con EP severas.

- La decisión de tratar la EP está basada en la severidad de los signos clínicos y el gradiente de presión a través de la válvula pulmonar. La valvuloplastia con balón es el procedimiento de elección en la EP severa. En las formas de EP tipo A el beneficio de la reducción de la obstrucción a largo plazo es mayor que en los perros con hipoplasia del anillo pulmonar.

**Estudio Clínico**

Se efectuó un estudio restrospectivo en 24 perros diagnosticados de EP congénita (no se incluyeron animales con otros defectos asociados) con el fin de correlacionar determinados
signos resultantes de la evaluación clínica con el gradiente de presión Doppler. A cada animal se le efectuó una historia clínica completa, examen físico, electrocardiograma, radiografías torácicas y examen ecocardiográfico completo.

Los criterios de diagnóstico de la EP fueron los siguientes: soplo sistólico mediante la auscultación torácica, visualización de la lesión anatómica obstructiva mediante ecocardiografía y la identificación de un flujo pulmonar turbulento con Vmáx > 1.6 m/sg.

Las principales conclusiones fueron las siguientes:
- La distribución por sexos fue similar (13 machos y 11 hembras).
- Edad al diagnóstico: 10 perros se diagnosticaron antes de los 6 meses, 8 perros entre 7 y 12 meses y 6 animales a partir de los 13 meses.
- Signos clínicos: 14 perros fueron asintomáticos al diagnóstico y 10 presentaron síncope y/o intolerancia al ejercicio y/o fallo cardíaco congestivo (ascitis).
- En 18 perros la EP fue clasificada como tipo A, 4 como tipo B y 2 de aspecto intermedio.
- El análisis de varianza puso de manifiesto una correlación positiva estadísticamente significativa (p>0.05) entre el gradiente de presión Doppler y signos clínicos, signos de agravamiento ventricular derecho en el ECG y parámetros radiográficos.

BIBLIOGRAFIA
CASE REPORT

Percutaneous occlusion of a muscular ventricular septal defect with an Amplatzer® Muscular VSD occluder

Marco L. Margiocco, DMV*, Barret J. Bulmer, DVM, MS, D. David Sisson, DVM

Department of Clinical Sciences, College of Veterinary Medicine, Oregon State University, Magruder Hall, Corvallis, OR, USA

Received 10 January 2008; accepted 11 January 2008

KEYWORDS
Dog;
Congenital heart disease;
Interventional;
Catheter

Abstract Ventricular septal defects are a relatively common congenital cardiac disease that, when severe, can be associated with substantial morbidity and mortality. Several minimally invasive methods of repair have been described in the human literature. This report describes the first case of percutaneous closure of a naturally occurring muscular septal defect using an Amplatzer® occluder in a dog affected by concurrent pulmonic stenosis. Based on this experience catheter-based occlusion of muscular ventricular septal defects is a feasible option in dogs. Further studies are necessary to identify the attributes and limitations of the technique. Published by Elsevier B.V.

* A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based images permitting the detailing of procedures and diagnostics that previously were limited with still figures. These images can be viewed (by those readers with subscription access) by going to http://www.sciencedirect.com/science/journal/17602734. The issue to be viewed is clicked and then the (blue) article title. Any supplementary material (including videos) is indicated in the article outline. A click on this heading leads to the video which can then be downloaded. Downloading the videos may take several minutes. It is anticipated that most users will have the relevant software or plug-ins to view videos online. Next to each multimedia (video) file there is a little ‘Help’ feature that explains how to “play” that particular file. Another means to view the material is to go to www.doi.org and enter the below doi number unique to the paper. If videos do not play, readers are advised to download one of the many freeware video player programmes available such as VLC media centre (www.videolan.org/vlc/).

* Corresponding author.
E-mail address: mmargioc@vet.k-state.edu (M.L. Margiocco).

1760-2734/$ - see front matter Published by Elsevier B.V.
doi:10.1016/j.jvc.2008.01.001
A seven-month-old, 4.9 kg, male Cavalier King Charles Spaniel was referred to the Oregon State University Veterinary Teaching Hospital Cardiology Service for evaluation and treatment of suspected pulmonic stenosis. Medical history included a cardiac murmur and moderate exercise intolerance associated with shortness of breath. At the time of presentation the dog was receiving atenolol (0.2 mg/kg PO BID).

Physical examination revealed a grade 5/6 left basilar systolic murmur that radiated to the right hemithorax. The dog manifested a positive hepatojugular reflux, pink mucous membranes and a capillary refill time of less than 2 sec. The femoral pulses were judged to be normal. An electrocardiograma showed sinus rhythm with a heart rate of 125 beats per minute and a marked right axis deviation with notched Q waves in Lead I. No cardiac arrhythmias were noted. Thoracic radiographs showed evidence of right ventricular enlargement, loss of the cranial waist of the cardiac silhouette suggesting an enlarged pulmonary artery and pulmonary hypo-perfusion. Two-dimensional echocardiographyb showed normal left heart dimensions and dilation of the right ventricular chamber with substantially increased wall thickness. Right atrial dimensions were normal. A large ventricular septal defect (VSD) was seen from the right parasternal short axis view in the anterior portion of the muscular interventricular septum, at the level of the chordae tendineae (Fig. 1). The maximum diameter of the VSD, as estimated from the short axis view, was approximately 9 mm. Color flow Doppler interrogation indicated bidirectional shunting. The presence of valvular pulmonic stenosis was evidenced by systolic doming of the pulmonary valve leaflets, suggestive of apical fusion of the cusps. Continuous wave Doppler interrogation of the right ventricular outflow tract documented a peak systolic velocity of 5.6 m/sec with a superimposed dynamic right ventricular outflow tract obstruction, characterized by a peak velocity of 3.6 m/sec (Fig. 2). Modest pulmonic insufficiency was also observed with a peak velocity (1.8 m/sec) suggesting normal pulmonary artery pressure. There was trivial tricuspid insufficiency.

Large muscular VSDs are usually associated with marked left-to-right shunting, pulmonary overcirculation, and left ventricular volume overload, commonly leading to left-sided congestive heart failure early in life. In this case the presence of pulmonic stenosis presumably limited the severity of left-to-right shunting, mimicking a palliative pulmonary artery banding intervention. The assessment of the severity of a stenotic lesion, purely based on the peak flow velocity, has several limitations. In this particular case the presence of an elevated velocity proximal to the stenotic valve would require the adoption of the "expanded Bernoulli formula", which takes into account the velocity upstream to the lesion, as well as the peak velocity through the obstruction itself (Table 1). The adoption of the simplified Bernoulli formula in fact would lead to a significant overestimation of the gradient through the stenotic valve. With this approach we estimated that the valvular component of the stenosis was only mild in severity. However, we documented right-to-left shunting of blood when the patient was agitated and

---

a PageWriter XLI, M1700A Cardiograph, Philips Medical Systems, Andover, MA.
b Vivid 7 Dimension Cardiovascular Ultrasound System, GE Healthcare, Milwaukee, WI.
setc was placed in the right carotid artery and vein and carotid artery. A 4 Fr introducer-dilator followed by surgical approach to the right jugular was premedicated with midazolam (0.05 mg/kg IV) and maintained with fentanyl (0.005 mg/kg IV) and midazolam (0.05 mg/kg IV) and maintained with 2% isoflurane in 100% oxygen. Preoperative skin incision was made to the right carotid artery and a selective angiogram was performed to assess the anatomy and the size of the defect. The angiogram showed moderate left-to-right shunting across a large VSD in the upper septum. The angiogram also allowed visualization of a small muscular VSD located in the apical portion of the left ventricle that was not detected on the echocardiogram. The smaller defect was judged hemodynamically insignificant and closure was not attempted. A 6 Fr angiographic catheter was introduced into the right ventricle and a selective angiogram recorded. The study showed moderate right ventricular concentric hypertrophy with moderate chamber dilation without evidence of tricuspid regurgitation. Dynamic infundibular and valvular pulmonic stenosis were identified together with post-stenotic dilation of the pulmonary artery. The large muscular VSD was visualized during both the levo- and dextro-phases, while the small apical VSD was appreciated only during the left-side phase of the angiogram. The diameter of the pulmonary artery annulus was estimated at 9 mm. The maximum diameter of the VSD was estimated at 10 mm. Immediately thereafter, a 4 Fr angiographic catheter was inserted into the right ventricle and, with the aid of a flexible guidewire, the VSD was crossed. The catheter allowed the positioning of an exchange guidewire that was used to guide a 7 Fr guiding catheter through the defect for delivery of the expandable occlusion device. During the manipulation of the guiding catheter within the right ventricle the patient experienced a short period of ventricular tachycardia followed by cardiac arrest. At the time of arrest the catheter displayed a wide curve, aiming towards the dorsal aspect of the interventricular septum possibly “stretching” the right ventricular wall. The catheter was promptly removed and cardiopulmonary resuscitation.

Transcatheter occlusion of the VSD was attempted with the intention to perform balloon valvuloplasty immediately after. The decision to perform VSD occlusion first was dictated by the risk of creating a life-threatening left-to-right shunt as a result of decreasing the right ventricular resistance to ejection via a successful balloon valvuloplasty. The patient was premedicated with midazolam (0.25 mg/kg IV) and oxymorphone (0.1 mg/kg IV). Anesthesia was induced with etomidate (2 mg/kg IV), fentanyl (0.005 mg/kg IV) and midazolam (0.05 mg/kg IV) and maintained with 2% isoflurane in 100% oxygen. Preoperative skin preparation of the ventral aspect of the neck was followed by surgical approach to the right jugular vein and carotid artery. A 4 Fr introducer-dilator set was placed in the right carotid artery and an 8 Fr introducer-dilator set was placed in the right jugular vein. Initially a 5 Fr sizing catheter was advanced under fluoroscopic guidance via the carotid artery and temporarily positioned in the ascending aorta to allow the calculation of a numeric factor to correct for image magnification. A 4 Fr angiographic catheter was advanced into the left ventricle and a left ventricular selective angiogram (Video 1) was performed in order to assess the anatomy and the size of the defect. The angiogram showed moderate left-to-right shunting across a large VSD in the upper septum. The angiogram also allowed visualization of a small muscular VSD located in the apical portion of the left ventricle that was not detected on the echocardiogram. The smaller defect was judged hemodynamically insignificant and closure was not attempted. A 6 Fr angiographic catheter was introduced into the right ventricle and a selective angiogram recorded. The study showed moderate right ventricular concentric hypertrophy with moderate chamber dilation without evidence of tricuspid regurgitation. Dynamic infundibular and valvular pulmonic stenosis were identified together with post-stenotic dilation of the pulmonary artery. The large muscular VSD was visualized during both the levo- and dextro-phases, while the small apical VSD was appreciated only during the left-side phase of the angiogram. The diameter of the pulmonary artery annulus was estimated at 9 mm. The maximum diameter of the VSD was estimated at 10 mm. Immediately thereafter, a 4 Fr angiographic catheter was inserted into the right ventricle and, with the aid of a flexible guidewire, the VSD was crossed. The catheter allowed the positioning of an exchange guidewire that was used to guide a 7 Fr guiding catheter through the defect for delivery of the expandable occlusion device. During the manipulation of the guiding catheter within the right ventricle the patient experienced a short period of ventricular tachycardia followed by cardiac arrest. At the time of arrest the catheter displayed a wide curve, aiming towards the dorsal aspect of the interventricular septum possibly “stretching” the right ventricular wall. The catheter was promptly removed and cardiopulmonary resuscitation.

Transcatheter occlusion of the VSD was attempted with the intention to perform balloon valvuloplasty immediately after. The decision to perform VSD occlusion first was dictated by the risk of creating a life-threatening left-to-right shunt as a result of decreasing the right ventricular resistance to ejection via a successful balloon valvuloplasty. The patient was premedicated with midazolam (0.25 mg/kg IV) and oxymorphone (0.1 mg/kg IV). Anesthesia was induced with etomidate (2 mg/kg IV), fentanyl (0.005 mg/kg IV) and midazolam (0.05 mg/kg IV) and maintained with 2% isoflurane in 100% oxygen. Preoperative skin preparation of the ventral aspect of the neck was followed by surgical approach to the right jugular vein and carotid artery. A 4 Fr introducer-dilator set was placed in the right carotid artery and an 8 Fr introducer-dilator set was placed in the right jugular vein. Initially a 5 Fr sizing catheter was advanced under fluoroscopic guidance via the carotid artery and temporarily positioned in the ascending aorta to allow the calculation of a numeric factor to correct for image magnification. A 4 Fr angiographic catheter was advanced into the left ventricle and a left ventricular selective angiogram (Video 1) was performed in order to assess the anatomy and the size of the defect. The angiogram showed moderate left-to-right shunting across a large VSD in the upper septum. The angiogram also allowed visualization of a small muscular VSD located in the apical portion of the left ventricle that was not detected on the echocardiogram. The smaller defect was judged hemodynamically insignificant and closure was not attempted. A 6 Fr angiographic catheter was introduced into the right ventricle and a selective angiogram recorded. The study showed moderate right ventricular concentric hypertrophy with moderate chamber dilation without evidence of tricuspid regurgitation. Dynamic infundibular and valvular pulmonic stenosis were identified together with post-stenotic dilation of the pulmonary artery. The large muscular VSD was visualized during both the levo- and dextro-phases, while the small apical VSD was appreciated only during the left-side phase of the angiogram. The diameter of the pulmonary artery annulus was estimated at 9 mm. The maximum diameter of the VSD was estimated at 10 mm. Immediately thereafter, a 4 Fr angiographic catheter was inserted into the right ventricle and, with the aid of a flexible guidewire, the VSD was crossed. The catheter allowed the positioning of an exchange guidewire that was used to guide a 7 Fr guiding catheter through the defect for delivery of the expandable occlusion device. During the manipulation of the guiding catheter within the right ventricle the patient experienced a short period of ventricular tachycardia followed by cardiac arrest. At the time of arrest the catheter displayed a wide curve, aiming towards the dorsal aspect of the interventricular septum possibly “stretching” the right ventricular wall. The catheter was promptly removed and cardiopulmonary resuscitation.

### Table 1

<table>
<thead>
<tr>
<th>Equation Type</th>
<th>Pre-intervention (mmHg)</th>
<th>Post-intervention (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplified Bernoulli equation</td>
<td>( PG = 4 \times (v_1^2) = 4 \times (5.6)^2 = 125.44 )</td>
<td>( PG = 4 \times (v_2^2) = 4 \times (3.2)^2 = 40.96 )</td>
</tr>
<tr>
<td>”Expanded” Bernoulli equation</td>
<td>( PG = 4 \times (v_2 - v_1)^2 = 4 \times (5.6 - 3.6)^2 = 16 )</td>
<td>( PG = 4 \times (3.2 - 2.0)^2 = 5.76 )</td>
</tr>
</tbody>
</table>

Data pre- and post-intervention are shown. PG = pressure gradient; \( v_1 \) = velocity of blood proximal to the pulmonic valve (dynamic RVOT obstruction); and \( v_2 \) = velocity of the blood at the level of the pulmonic valve.

---

\( ^{c} \) Check-Flo® Performer® 4F and 5F Introducer sets, Cook Inc., Bloomington, IN.

\( ^{d} \) Royal Flush® II 5F, 70 cm Angiographic Sizing Catheter, Cook Inc., Bloomington, IN.

\( ^{e} \) Torcon NB® Advantage 5 Fr, 110 cm Pigtail Angiographic Catheter, Cook Inc., Bloomington, IN.

\( ^{f} \) Berman 6 Fr, 90 cm Angiographic Balloon Catheter, Arrow International Inc., Reading, PA.

\( ^{g} \) Infinity™ Right Judkins 3.5, 4 Fr, 100 cm Diagnostic Catheter, Cordis Corp., Miami, FL.

\( ^{h} \) Wire Guide PTFE coated straight 0.035", 145 cm, Cook Inc., Bloomington, IN.

\( ^{i} \) Wire Guide TFE coated curved 0.035", 145 cm, Cook Inc., Bloomington, IN.

\( ^{j} \) MPA-1 7 Fr, 100 cm Multipurpose Guiding Catheter, Cordis Corp., Miami, FL.

\( ^{k} \) Amplatzer™ Muscular VSD occluder, device waist size 10 mm, AGA Medical Corp., Golden Valley, MN.
consisting of external cardiac massage, intravenous epinephrine (0.05 mg/kg IV) and atropine (0.05 mg/kg IV), was instituted. A subsequent period of sustained ventricular tachycardia was successfully treated with intravenous lidocaine (2 mg/kg IV). The procedure was aborted and the patient was monitored during recovery from anesthesia in the intensive care unit. Cortical blindness was present for 12 h, associated with moderate ataxia and lethargy. The patient completely recovered in 36 h and was dismissed to the care of the owner 48 h after recovery from anesthesia.

We elected a different approach in a second attempt three weeks later. A similar vascular approach was performed, this time using the left jugular vein and left carotid artery. Right and left ventricular angiograms were recorded using the same technique as previously described. The pulmonary valve was then partially dilated with a 6 mm and subsequently an 8 mm valvuloplasty balloon catheter. This partial dilation was performed in an attempt to reduce the right ventricular afterload, hopefully making the chamber less sensitive to the mechanical stress of catheterization. Following the valvuloplasty procedure, the VSD was crossed using a 4 Fr Judkins right catheter with the aid of a flexible guidewire. An exchange guidewire was then positioned through the defect and a 6F curved sheath was advanced over the exchange guidewire. The guidewire and the internal guiding catheter were removed and a 10 mm self-expandable Amplatzer Muscular VSD occluder was advanced through the sheath. The distal disc of the device and part of the waist were deployed in the left ventricle and the sheath was retracted until the disc came in apposition with the interventricular septum. Thereafter, the remaining part of the waist and the proximal disc were fully deployed, with the device still attached to the delivery wire. Gentle movements of the delivery wire allowed the alignment of the device within the defect. Immediately after delivery, the right disc did not acquire a completely flat configuration, most likely as a result of the sharp angle between the defect and the delivery system. However, the configuration was judged stable. A 4 Fr angiographic catheter was used to record left ventricular and aortic root angiograms immediately after deployment of the device. Mild residual flow through the septal defect and absence of aortic insufficiency were documented. The device was judged to be correctly positioned, was released from the delivery wire, and a final balloon valvuloplasty was performed using a 10 mm balloon valvuloplasty catheter. No significant indentation of the balloon was noticed during inflation, suggesting that the first two dilations had successfully separated or torn the fused leaflets. The dog recovered uneventfully from anesthesia. Post-procedural thoracic radiographs showed the device was appropriately positioned, with both discs expanded. An echocardiogram was performed immediately after and 24 h after the procedure. No residual flow through the VSD was observed in either study. The velocity of blood flow through the pulmonary valve was reduced to 3.2 m/sec, with a dynamic RVOT velocity of about 2.0 m/sec (Table 1). There was trivial tricuspid insufficiency and mild mitral insufficiency. The dog was dismissed on oral antibiotics (cephalexin, 22 mg/kg PO BID) for a week and the beta-blocker (atenolol, 0.5 mg/kg PO BID) was continued. Short-term follow-up evaluations have not been possible because the owner relocated out of state. Several telephone interviews with the owner indicate that the clinical signs have resolved and no adverse events have been observed. Approximately two years after the procedure the dog was evaluated at Kansas State University VMTH by one of the authors (MLM). At that time the owner confirmed the absence of clinical signs.
radiographs were obtained that showed the device was in place with no changes in its morphology. An echocardiogram showed the absence of residual flow through the VSD, as documented by color-Doppler. There was no detectable dynamic RVOT obstruction and the residual valvular pulmonic stenosis was mild, based on spectral-doppler interrogation of the transvalvular jet (peak velocity 3.0 m/sec).

Discussion

Ventricular septal defects consist of an abnormal communication, most commonly congenital in origin, between the right and the left ventricle that can occur at different levels of the interventricular septum. They represent 12% of all canine congenital heart defects and are the most common congenital cardiac disease in children. The most common type of VSD in dogs is the membranous VSD, entirely located within the membranous portion of the interventricular septum. These defects often partially extend to the dorsal aspect of the muscular septum and are referred to as perimembranous VSDs. Muscular VSDs, encountered infrequently in dogs, are entirely located within the muscular or trabecular septum and can occur in different locations, as isolated or multiple defects. These defects often partially extend to the dorsal aspect of the muscular septum and are referred to as perimembranous VSDs. Muscular VSDs, encountered infrequently in dogs, are entirely located within the muscular or trabecular septum and can occur in different locations, as isolated or multiple defects. The hemodynamic consequences of a VSD principally depend on the size of the defect, the ratio of systemic to pulmonary vascular resistance and the presence of other congenital or acquired cardiovascular diseases. As a result of these complex interactions different clinical scenarios can occur, dictating different treatment strategies. When closure of the defect is indicated, there are two options, surgery or transcatheter delivery of an occluding device in a minimally invasive fashion. A variety of devices have been used for the occlusion of VSDs in human patients and in experimental animal models, including detachable inflatable balloons, Gianturco coils, the Rashkind double umbrella, Bard Clamshell, Button device and, most recently, the Amplatzer VSD occluders. Several reports on percutaneous treatment of experimentally-induced VSDs in canine models have been published, describing the use of different occlusion devices. Only two reports on percutaneous treatment of spontaneously occurring VSDs have been published. In these reports a total of four dogs with naturally occurring VSDs of the perimembranous type were treated with transcatheter coil embolization, using detachable coils designed for PDA occlusion. In two of these dogs, a second intervention with delivery of one or two additional coils was performed because of the presence of significant residual flow. No major complications were described.

Amplatzer VSD occluding devices are currently manufactured in three different models, specifically designed for the treatment of membranous VSDs, muscular congenital VSDs, and muscular acquired (post-myocardial infarction) VSDs. The frame of these devices is composed of nitinol, a nickel–titanium alloy with several properties that make it ideal for implantable devices. It has remarkable shape-memory that allows a total spontaneous reshaping of the device once it is deployed from the delivery catheter. It is biocompatible and does not undergo significant corrosion when implanted. The device has right and left retention discs connected by a waist. It can be secured to a delivery wire by means of a small screw and, after proper positioning, released in place. It has proved highly efficacious in closing muscular VSDs experimentally created in dogs. Clinical trials in human patients have been performed and the device has been approved for use in Europe and the USA.

This case report shows that minimally invasive, transcatheter occlusion of muscular VSDs is feasible in canine clinical patients. The long-term integrity of the device is unknown but the technique is certainly promising. The technical challenges encountered during the procedure were judged to be, at least in part, due to the coexistence of pulmonic stenosis, the small size of the dog, and the performance of a new technique. The left anterior oblique view is considered the best angiographic view for the visualization of a VSD located in the anterior muscular septum. The adoption of this view could have improved the visualization of the defect, but the lateral view adopted during the procedure was considered satisfactory. As a consequence of the small size of the patient compared to the size of the device, and the sharp angle between the delivery system and the defect itself, the expansion of the distal disc occurred in close proximity to the mitral valve apparatus, leading to potential risk of damage to the valve leaflets or chordae tendineae. Although no major mitral regurgitation was noticed after the procedure, this risk should be considered in future procedures, and any attempt to obtain a better alignment between the defect and the delivery catheter should be made, such as the adoption of a differently shaped catheter or a different approach (femoral vein instead of jugular vein), depending on the size of the patient and location of the defect. Furthermore, the potential benefit of adopting a hybrid procedure (combination of mini-thoracotomy and trans-mycardial catheter-based approach) should be investigated and considered in small size patients.
larger scale studies, including extended follow-up and potentially membranous/perimembranous defects, will be necessary to further optimize the technique in clinical patients and understand the long-term outcome of this procedure.

Acknowledgements

The authors wish to thank Dr. Kurt Amplatz and Dr. Xiaoping Gu, AGA Medical, for donating the Amplatzer® mVSD occluding device and delivery system. Special gratitude goes to Dr. Craig Mosley, Dr. Conny Gunkel and Dr. Daniel Pang for providing anesthesia support and to Ms. Robyn Ostapkovicz-Panico, CVT, for technical assistance.

References


Available online at www.sciencedirect.com