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A study on the risk of subaortic and pulmonic stenosis and on genetic aspects of echocardiography measurements in the Italian Boxer dog

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RIASSUNTO – Studio sul rischio di insorgenza di stenosi subaortica e polmonare e sugli aspetti genetici delle misure ecocardiografiche nel Boxer italiano. *Le stenosi subaortica (SAS) e polmonare (PS) sono difetti cardiaci che colpiscono diverse razze canine. Il presente studio si prefigge lo scopo di quantificare la loro prevalenza, indagare la variabilità del soffio auscultato e delle misurazioni ecocardiografiche, valutare il rischio di stenosi attraverso un'analisi di regressione logistica e stimare il coefficiente di ereditabilità di alcune variabili ecocardiografiche. Gli esami ecocardiografici sono stati condotti da 7 veterinari cardiologi su 1283 cani. In circa il 70% dei boxer il soffio è stato classificato assente o fisiologico, nel 21,6% moderato e grave nel 8,6%. I modelli lineari impiegati hanno spiegato dal 4 al 38% della variabilità dei caratteri morfometrici, ma solo dal 2,2 al 6,7% della variabilità dei dinamici. L'analisi logistica ha dimostrato il ruolo di soffio, velocità di picco e dimensioni degli osti valvolari quali fattori di rischio per l'evento stenosi. I valori di ereditabilità stimati variano tra l'8,7 ed il 33,7%.*

KEY WORDS: boxer, subaortic stenosis, pulmonic stenosis, heritability.

INTRODUCTION – Subaortic and pulmonic stenosis are congenital cardiac defects affecting several dog breeds (Jacobs, 1990; Buchanan, 1992; Tidholm, 1997). Subaortic stenosis (SAS) is characterized by a fibrous ring of tissue placed immediately below the aortic valve. Pulmonic stenosis (PS) consists on a narrowing placed anywhere from the right ventricular outflow tract to the main pulmonary artery (MPA) (Kittelson and Kienle, 1998). Moderate-to-severe SAS and PS can impair dog's life quality. Pharmacological therapy is palliative, while surgical operations, albeit resolutive, are traumatic, hazardous and expensive. Studies investigating genetic and non-genetic aspects of cardiac abnormalities could aid to prevent occurrence of heart defects.
This study aimed to assess prevalence of SAS and PS in the Italian Boxer dog population, to investigate variation of cardiac murmur grade and echocardiography measurements, to perform a risk analysis of heart defects through logistic regression and to obtain heritability estimates of the main echocardiography measurements. The Boxer breed was chosen because reported as being at increased risk of developing congenital heart diseases, with SAS being the most frequent finding (Bussadori *et al.*, 2001).

MATERIAL AND METHODS – The study was performed using data from 1283 random Italian Boxer dogs (53.6% females and 46.4% males) which underwent a complete echocardiographic examination carried out by 7 veterinarians from 1999 to 2004.
The SAS lesions (2D images) were classified according to the Pyle-Patterson criteria (Pyle *et al.*, 1976) in three classes: *Grade 1*: variable number of small (1 to 2 mm) whitish, slightly raised nodules on the endocardial sur-

face of the interventricular septum immediately below the aortic valve and on the ventral surface of the aortic valve cusps; *Grade 2*: narrow ridge of whitish, thickened endocardium extended partially around the left ventricular outflow tract (LVOT); *Grade 3*: fibrous band, ridge or collar completely encircling the LVOT just below the aortic valve. PS has been classified according to Bussadori *et al.* (2001) into two classes: *Type A*: normal annular size, moderate to severe commissural fusion and moderate thickening of valve leaflets, often associated with post-stenotic dilation of the MPA, not correlated with the severity of the obstruction; *Type B*: hypoplasic pulmonary ostium, immobile severely thickened valvular leaflets and uncommon post-stenotic dilation of the MPA. The clinical diagnosis was based on anatomical lesions assessed through echocardiography, peak velocity (aortic more than 2 m/s, pulmonary more than 1.8 m/s) and turbulent flow (distal to the Valsalva sinus for SAS and into the proximal MPA for the PS). Thereafter, according to the peak gradient between aorta and left ventricle or between the MPA and right ventricle, (calculated from the peak velocity using the simplified Bernoulli equation), the stenoses were classified as: *mild* (from 20 to 50 mmHg corresponding to a velocity of 2.25-3.5 m/s), *moderate* (from 50 to 80 mmHg corresponding to a velocity of 3.5-4.5 m/s) and *severe* (over 80 mmHg corresponding to a velocity over 4.5 m/s) (Bussadori *et al.*, 2000).

Data were analysed in order to obtain descriptive statistics of traits considered. A logarithmic transformation of the peak velocities was performed because of their unsymmetrical distribution. Morphometric and dynamic traits were analysed through GLM procedure of SAS package (1990) according to the fixed effects of the veterinarian, of the gender and of the body weight of the dogs. The morphometric traits were adjusted for body weight and operator effects, and the dynamic traits for the operator effect only. Adjusted traits were then standardized and allotted into three classes according to standard deviation (<-0.75 sd units; -0.75 and 0.75 sd units; >0.75 sd units). The murmur was graded according to the Levine's heart murmur grading system and expressed as absent or physiological (grade I), mild (grade II) and severe (grade III or higher).

Logistic regression analysis (SAS package, 1990) was performed in order to provide odds ratio, expressing the relative risk of SAS or PS occurrence due to standardized morphometric and dynamic traits and murmur grade with respect to the "reference dog", i.e. the intercept of the logistic regression model. In this study was taken as reference the dog exhibiting an absent or physiological murmur (grade I), an average live weight and belonging to the lowest classes for all morphometric and dynamic traits.

Pedigree data and variance components estimated by VCE software (Groenelveld, 1990) were finally used to obtain estimates of heritability for the main echocardiography traits. Mixed linear models used for estimating variance components included non-genetic effects previously described and the additive genetic effect of dogs and took into account all known additive relationships (3825 dogs).

RESULTS AND CONCLUSIONS – Prevalence of SAS and of PS was 9.5 and 4.1%, respectively, and mild class of severity was the most frequent in both diseases. The 69.8% of the boxers presented absent or physiological murmur, 21.6% mild and 8.6% severe (data not shown in tables).

Table 1. Descriptive statistics of data set.

variable	mean	standard deviation
age (months)	23.926	13.538
weight (kg)	29.821	4.744
aortic annulus (cm)	1.741	0.197
pulmonary annulus (cm)	1.739	0.221
aortic peak velocity logarithm	0.714	0.233
pulmonary peak velocity logarithm	0.335	0.238
aortic peak gradient (mmHg)	19.509	18.580
pulmonary peak gradient (mmHg)	9.189	9.224

Descriptive statistics for age, body weight and main echocardiography traits are given in Table 1. On average, age at examination approached 2 years, and weight of dogs was close to 30 kg.

The linear models applied to morphometric variables explained from 4.4 to 38% of variation, whereas the mod-

els used for the dynamic variables explained only from 2.2 to 6.7% of variation. Body weight and veterinarian significantly affected the morphometric traits, whereas only veterinarian effect was significant for the dynamic ones. From logistic regression analysis, murmur grade, peak velocity and orifice diameter significantly affected the risk of SAS occurrence; similarly, murmur grade, peak velocity and gender significantly influenced PS clinical diagnosis.

Peak velocities were the most important risk factor for both diseases, followed by the murmur grade ($P<0.001$). Namely, the probability of a positive diagnosis for stenosis increased at increasing velocities and murmur grade. Concerning the relationship between aortic orifice diameter ($P<0.1$) and disease occurrence, the probability of a positive diagnosis raised at narrowing aortic orifice. Another risk factor for PS occurrence was gender ($PS<0.05$): a positive diagnosis for PS seemed to be more probable in male dogs.

Heritability estimates and additive genetic variance for echocardiography traits are given in table 2. Heritability for morphometric traits was 23 and 18% for aortic and pulmonary annulus, respectively. Heritability estimates were moderate for dynamic traits too, and ranged between 19 and 25%. Standard errors of estimates were low for all traits of concern.

Table 2. Heritability estimates of some of the studied echocardiography traits.

trait	h^2 (%)	σ_a^2	SE (%)
aortic annulus	23	0.006	0.05
pulmonary annulus	18	0.006	0.049
aortic peak velocity	24.9	0.09	0.059
pulmonary peak velocity	18.6	0.04	0.051
aortic peak gradient	20.8	56.274	0.059
pulmonary peak gradient	18.7	16.268	0.051

In conclusion, results from this study confirm the moderate prevalence of SAS and the low prevalence of PS in the Italian Boxer dog population. Probably, the progressive nature of these cardiac defects and the sudden death in the severely affected dogs could explain the highest frequency of the mild forms found in this survey. Body weight and veterinarian skill appeared important sources of variation of ecocardiography traits, suggesting the importance of a specific training of operators and a standardized approach to the echocardiographic procedure in order to obtain comparable studies with little inter and intra-operator variability. The logistic regression analysis results support the role of auscultation as a screening tool for congenital heart defects. Ecocardiography traits showed moderate but consistent estimates of heritability and significantly affected the risk of cardiac diseases. These could ensures feasibility of selection programs aimed to reduce prevalence of cardiac diseases, provided that a regular screening program of Boxer dogs is performed.

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