Survival, risk factors and the effect of pulmonary balloon valvuloplasty in dogs with pulmonic stenosis: a retrospective study

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Abstract

***Objectives*:** To assess survival and potential risk factors in dogs with moderate (Doppler gradient 50-80 mmHg) and severe (Doppler gradient >80 mmHg) valvular pulmonic stenosis and to evaluate the effect of pulmonary balloon valvuloplasty (PBV) on survival in these dogs.

***Materials and methods*:** A retrospective study. Medical records of dogs with valvular pulmonic stenosis (PS) and a Doppler gradient (DG) >50 mmHg, undergoing pulmonary balloon valvuloplasty or not at the University Clinic for Companion Animal Health in Utrecht between April 2005 and September 2018, were reviewed. Owners and/or veterinarians were contacted to obtain information about the current status of the patients. Several dogs have revisited the clinic for an echocardiologic recheck. Twenty-eight dogs were excluded due to incomplete follow-up or concurrent significant diseases. Patients receiving atenolol were not excluded. Survival curves, univariate analyses and multivariate analyses have been performed on the overall population and on subgroups.

***Results*:** One hundred and twelve cases were included. Twenty dogs had moderate pulmonic stenosis (mean DG 66 mmHg, sd 7.3) and 92 dogs had severe pulmonic stenosis (median DG 112 mmHg, I/Q 92.3-148.8). Seventy-four dogs had type A pulmonic stenosis, 18 dogs type B, 10 dogs an intermediate type and 10 dogs type unknown. In 64 dogs PBV was performed (median DG 107.5, I/Q 64.6-143) and 48 dogs did not undergo the procedure (median DG 104, I/Q 75.8-132.7). PBV positively affects survival in the overall population (HR 0.361, P=0.047) and in dogs with severe pulmonic stenosis (HR 0.269, P=0.011). It reduced median DG with 51.6% (52 mmHg, I/Q 39.7-76) in the overall population. Two dogs died during the procedure. The calculated four-year survival of dogs in the overall population undergoing PBV is 93.7% and in dogs not undergoing the procedure 67.6%. In dogs with severe pulmonic stenosis undergoing PBV and not undergoing the procedure four-year survival is 93.1% and 59.2%, respectively. Factors negatively affecting survival in our study population are the pulmonary Doppler gradient (total population: HR 1.013, P=0.024; severe PS group: HR 1.014, P=0.034), older age at diagnosis (total population: HR 1.020, P=0.027; severe PS group: HR 1.020, P=0.023), the presence of clinical signs (total population: HR 2.546, P=0.031; severe PS group: HR 2.494, P=0.046) and the presence of tricuspid regurgitation (total population: HR 3.579, P=0.005; severe PS group: HR 3.167, P=0.014). Risk factors in dogs undergoing PBV were the pulmonary Doppler gradient (HR 1.022, P=0.029), older age at diagnosis (HR 1.033, P=0.006) and valve morphology type B (HR 7.026, P=0.025). In dogs not undergoing PBV the pulmonary Doppler gradient (HR 1.019, P=0.021) and the presence of clinical signs (HR 3.287, P=0.025) negatively affected survival. The group of dogs with moderate pulmonic stenosis was too small to perform analysis on.

***Conclusion*:** Pulmonary Doppler gradient, older age at the time of diagnosis, the presence of clinical signs and the presence of tricuspid regurgitation are risk factors for cardiac-related death in dogs with severe pulmonic stenosis. Valve morphology type B is a negative prognostic indicator in dogs undergoing PBV. PBV is confirmed to prolong survival in dogs with severe PS and is therefore the elective treatment in these patients.

Introduction

Pulmonic stenosis (PS) is one of the most commonly reported congenital heart defects in dogs, accounting for up to 20% to 32% of total congenital heart defects.[1, 2] It is mostly seen in Boxers, French and English bulldogs, small terrier breeds and mixed breeds. A slight male predisposition has been observed, although not significant.[1, 2]

PS is a congenital defect characterized by a narrowing of the right ventricular outflow tract. PS can be anatomically classified into three groups: supravalvular, valvular and subvalvular. Valvular stenosis is the most common form and can be classified into type A, type B or an intermediate type. Type A PS is the most common type and is characterized by mild or no thickening of the pulmonary valve with commissural fusion of the leaflets and minimal to no narrowing of the pulmonary valve annulus. Type B is characterized by moderate to severe thickening of the valve leaflet with minimal or no leaflet fusion, variable degrees of hypoplasia of the valve leaflets and in more severe cases hypoplasia of the pulmonary valve annulus. The intermediate type seems to be uncommon and contains characteristics of both types A and B.[1, 3-6]

A diagnosis is made by the use of echocardiography, during which the severity of the stenosis can be determined by measuring the Doppler-derived peak transvalvular pulmonary pressure gradient (DG). PS is considered mild when DG is between 10 and 49 mmHg, moderate when between 50 and 80 mmHg and severe when it is greater than 80 mmHg.[6]

Due to PS, secondary changes in the heart can develop. These include concentric hypertrophy of the right ventricle, poststenotic dilation of the main pulmonary artery segment, tricuspid valve regurgitation and right atrial enlargement. Clinical signs such as lethargy, exercise intolerance, syncope and ascites can develop.[5, 7]

Pulmonary balloon valvuloplasty (PBV) has become the primary treatment for valvular stenosis. It reduces the DG and alleviates clinical signs. It appears to be ineffective in supravalvular or subvalvular stenosis.[3, 8, 9] During the procedure a ballooned catheter is inserted through the jugular or femoral vein. Guided by fluoroscopy, it is placed into the pulmonary artery at the level of the stenosis and then inflated to reduce the waist of the stenosis.[3]

Dogs with mild valvular PS usually have a normal life span and show no clinical symptoms throughout life. PBV is not likely to benefit these patients.[3] In dogs with severe valvular PS (DG >80 mmHg) an intervention is recommended by veterinary cardiologists. PBV is considered the treatment of choice in these patients and, according to several studies, it alleviates clinical signs and prolongs survival significantly when compared to no treatment. Lower mortality rates were observed when PBV was performed and more dogs became asymptomatic or remained asymptomatic.[4, 8]

Recommendations regarding dogs with moderate valvular PS are not yet clear. In humans PBV is recommended when the DG is >50 mmHg.[10] In general, PBV is recommended in dogs with moderate stenosis that are symptomatic.[3] In one study it has been stated that dogs with a DG >60 mmHg may benefit from PBV.[11] The results of this study have however been questioned by others.[12] In another study PBV did not significantly increase survival in dogs with moderate PS.[4]

Several variables have been reported to affect survival in dogs with PS. Risk factors that have been described to influence survival are the presence of clinical signs, DG (severity), valve morphology (type), age at diagnosis, treatment (PBV or not) and the presence and severity of tricuspid regurgitation.[4, 11, 13]

To the authors knowledge, up to date, only one retrospective study has analyzed survival and long-term predictors affecting survival in a large population of dogs with moderate and severe PS. Dogs with severe PS undergoing PBV and asymptomatic dogs with moderate PS had a better outcome. Factors negatively affecting survival were DG, younger age at diagnosis, clinical signs and valve morphology type B.[4]

The primary objective of this study was to assess the survival in dogs with moderate and severe valvular PS and to evaluate the effect of PBV on survival in dogs referred to the University Clinic for Companion Animal Health in Utrecht between April 2005 and September 2018. Secondary objectives were evaluation of potential risk factors (clinical signs, DG, valve morphology, age at diagnosis and the presence of tricuspid regurgitation) affecting survival in this group of dogs.

Material and methods

The medical records of client-owned dogs with PS that visited the University Clinic for Companion Animal Health in Utrecht for cardiologic examination between April 2005 and September 2018 were retrospectively reviewed. Inclusion criteria were a diagnosis of moderate to severe PS (DG >50 mmHg), known valvular morphology and localization, the presence of a complete echocardiographic report, the dog's general data, clinical history and findings, treatment (PBV or no PBV) and medical therapy and a known follow-up. Dogs that simultaneously had other congenital heart disease

(CHD) without additional clinical signs and without being haemodynamically compromised (i.e. without significant pressure or volume overload) and dogs with other non-life-threatening non-cardiac diseases were also included in the study. Exclusion criteria were dogs with the presence of other CHD with additional clinical signs or that were haemodynamically compromised, dogs with other possible life-threatening non-cardiac diseases, incomplete medical records and incomplete or no follow-up. Dogs with characteristics of tricuspid valve dysplasia (TVD) according to the echocardiographic report were also excluded. The diagnosis of TVD was based on the criteria as described by Bussadori and Boon.[5, 6, 14] If the tricuspid valve apparatus morphology was considered normal, the presence of tricuspid regurgitation was assumed to be secondary to the pulmonic stenosis (due to dilation of the annulus of the tricuspid valve). Tricuspid regurgitation was graded mild, moderate or severe.

The diagnosis of PS was made by echocardiography by an ECVIM board-certified cardiologist (V. Szatmári) and three (at that time) ECVIM-cardiology residents (N. Beijerink, M.J.M. Dirven and M.L. den Toom). PS severity and valvular morphology were classified according to guidelines described by Boon, Bussadori and Chetboul.[5, 6, 14] PS was classified as type A when the pulmonic valve leaflets were normal to mildly thickened and demonstrated commissural fusion, when there was systolic doming and no pulmonary annulus hypoplasia (aortic/pulmonary annulus ratio ≤1.2).[5, 6, 13, 15] PS was classified as type B when the pulmonic valve leaflets were severely thickened and immobile and/or when pulmonary annulus hypoplasia was present. Annulus hypoplasia was defined when the aortic/pulmonary ratio was >1.2.[5, 6, 13, 15] Type B PS has been categorized into two groups by the authors: type B1 and type B2. Type B1 is defined as PS with severely thickened leaflets without the presence of annulus hypoplasia and type B2 as PS with both thickened leaflets and annulus hypoplasia. Intermediate type PS was defined when characteristics of both types (A and B) were present, such as commissural fusion and systolic doming in combination with mild annulus hypoplasia.[13] Types that could not be defined, e.g. due to a lack of good quality echocardiographic images or descriptions, have been categorized as type unknown.

Owners and/or veterinarians were contacted in order to obtain information about the current status of the patients. Information on whether the patient is dead or alive, the cause of death, the presence of clinical signs, the presence of other diseases, medical treatment and possible echocardiographic rechecks have been collected. All deaths, including sudden deaths and euthanasia due to worsening of right congestive heart failure (RCHF), were considered to be cardiac-related unless there was a clear non-cardiac cause of death.

Owners that were contacted were offered a free echocardiologic exam to see if there had been any changes since the last visit.

Statistical analysis

Data were analyzed using the statistics software SPSS Statistics 25. To indicate a statistical significance a P-value of <0.05 was taken in all cases. To analyze if there was normal distribution, a One-Sample Kolmogorov-Smirnov test was used. Data with normal distribution were expressed as mean ±standard deviation (sd). For data that were not normally distributed, the median and upper and lower interquartiles (I/Q) were given.

Survival was calculated as the period in days between the date of diagnosis and date of death or last visit/phone call. An event has been defined as cardiac-related death due to PS. This included sudden deaths and euthanasia due to clinical signs or RCHF. Dogs were censored when they were still alive or were euthanized or died for non-cardiac reasons. Animals lost to follow-up were censored and included in the survival analysis until the last date at which they were known to be alive. The Kaplan-Meier method and log-rank tests were used to compare time to event data between different groups. If the survival curves crossed, the Breslow test was used.

The influence of pulmonary DG, PS severity, treatment (PBV or not), clinical signs, valve morphology (type), TR, age at diagnosis and atenolol on survival was estimated by univariate and multivariate Cox proportional hazards analysis. Variables that showed a significant association of p<0.20 with the time to event in the univariable analysis were taken forward into a multivariable model, using the backward-stepwise method. The variable with the highest P-value was eliminated from the model until all variables in the model had a P-value of <0.05.

For analysis of the PBV and non PBV (NPBV) group type B1 and B2 have been combined, for the reason that there are too few patients of these separate types to perform a good analysis. In the overall population and in the severe PS group type B1 and B2 have been analyzed as separate types and as one type together (type B), to see if there would be a different outcome. No analysis could be performed on the moderate PS group, due to the reason that there are too few dogs in this group to perform analysis on.

The degrees of TR have not been assessed separately, as there were too few dogs with severe TR to perform good analysis on. Therefore, mild, moderate and severe TR have been combined into one group.

Results

Hundred and fifty-four dogs with a diagnosis of moderate and severe PS and a complete case record were selected. One hundred and forty-one dogs had valvular PS, 4 supravalvular PS and 9 subvalvular PS. Thirteen dogs with valvular PS had an incomplete follow-up and could therefore not be used in the survival study. Nine dogs were excluded because of concurrent haemodynamically significant CHD: 1 severe (8.0 m/s) subvalvular aortic stenosis (SAS), 1 double-chambered right ventricle, 1 ventricular septum defect (VSD), 1 untreated persistent ductus of Botalli (PDA), 3 tricuspid valve dysplasia and 2 had two or more CHD. Furthermore, 1 dog was excluded because of severe pulmonic hypertension and 1 dog because of a severe aortic valve insufficiency. Five puppies were excluded because they were euthanized due to a poor prognosis within 2 weeks after diagnosis.

The final study population included 112 dogs. Sixty-three dogs (56%) were male or male castrated and 49 dogs (44%) were female of female castrated. Thirty-seven breeds were represented. The most common type of breed was the French Bulldog (n=24), followed by mixed breeds (n=9), American Staffordshire Terriers (n=7), Nova Scotia Duck Tolling Retrievers (n=6), Rhodesian Ridgebacks (n=6), Boxer dogs (n=5) and Chihuahuas (n=5). Other breeds were represented by fewer than 5 dogs.

Twenty-four dogs (21%) with haemodynamically insignificant concurrent CHD have been included in the study: 1 mild aortic stenosis (2.6 m/s), 4 small patent foramen ovale (PFO), 4 small restrictive ventricular septum defects (VSD), 1 very small PDA, 1 small atrial septum defect (ASD), 1 persistent left superior vena cava, 2 mitral valve dysplasia and 2 showed multiple CHD (moderate restrictive VSD and mild PDA, VSD and mitral valve dysplasia). In 8 dogs a mildly increased flow velocity of the left ventricular outflow tract was observed (2.1 m/s to 2.44 m/s), which could not be further classified due to the retrospective nature of this study. The anatomy of these left outflow tracts showed no abnormalities. Three dogs showed hypoplasia of the aortic annulus (Bull Terrier and Boxer), a condition which has previously been described in these breeds.[16-18]

Eighty dogs (71%) had a definitive diagnosis of PS before one year of age, while 32 dogs (29%) were older than one year at the time of diagnosis. Median age was 5.6 months (I/Q: 3.4-15.9).

Type A morphology was observed in 66% of dogs (n=74) and type B in 16% (n=18), of which type B1 accounted for 4.5% (n=5) and type B2 for 11.5% (n=13). The intermediate type was diagnosed in 9% of dogs (n=10) and type unknown also in 9% (n=10). Moderate PS was diagnosed in 20 dogs (18%) and severe PS in 92 dogs (82%) (**Table 1**). Mean peak DG of the group of dogs with moderate PS was 66 mmHg (sd 7.3) and in the group with severe PS median peak DG was 112 mmHg (I/Q: 92.3-148.8).

Sixty-four dogs (57%) underwent PBV, of which 8 presented with moderate PS (12.5%) and 56 with severe PS (87.5%). Dogs with moderate PS all had a high moderate DG, varying from 61.6 mmHg to 78 mmHg. Median DG of the PBV group was 107.5 (I/Q: 64.6-143) before ballooning, which was reduced with 51.6% (52 mmHg, I/Q 39.7-76) after ballooning. Forty-eight dogs (43%) did not undergo PBV. Of this group 12 presented with moderate PS (25%) and 36 with severe PS (75%). Median DG of the NPBV group was 104 (I/Q: 75.8-132.7).

Twenty-six percent of dogs (n=29) showed clinical signs (exercise intolerance, syncope, ascites) in the NPBV group (n=15) and PBV group (n=14) before ballooning (**Table 2**). Twenty-five dogs with clinical signs had severe PS and 4 dogs with clinical signs had moderate PS. Only 2 dogs presented RCHF, both with severe PS. Seven dogs presented with more than one clinical sign.

Twenty-three dogs (20.5%) were diagnosed with TR. Seventeen dogs were diagnosed with mild TR, 5 dogs with moderate TR and 1 dog with severe TR.

Ten dogs with severe PS and 1 dog with moderate PS in the NPBV group and 11 dogs with severe PS and 1 dog

Table 1. Population characteristics

	Overall population	PBV group	NPBV group
Cases (n)	112	64	48
Median DG (mmHg)	105	107.5	104
Severe PS (n)	92 (82%)	56 (87.5%)	36 (75%)
Moderate PS (n)	20 (18%)	8 (12.5%)	12 (25%)
Type A PS (n)	74 (66%)	45 (70.3%)	29 (60.4%)
Type B1 PS (n)	5 (4.5%)	2 (3.2%)	3 (6.3%)
Type B2 PS (n)	13 (11.5%)	7 (10.9%)	6 (12.5%)
Type intermediate PS (n)	10 (9%)	3 (4.7%)	7 (14.5%)
Type unknown (n)	10 (9%)	7 (10.9%)	3 (6.3%)
Dogs with clinical signs (n)	29 (26%)	14 (22%)	15 (31.3%)
Dogs without clinical signs (n)	83 (74%)	50 (78%)	33 (68.7%)

Table 2. Clinical signs at presentation			
	Overall population	**PBV group**	**NPBV group**
Dogs showing clinical signs (n)	29	14	15
Exercise intolerance (n)	21	11	10
Syncope (n)	13	5	8
Ascites (RCHF) (n)	2	1	1

Table 3. Cardiac deaths among overall population, PBV group and NPBV group			
Cardiac deaths	**Overall population**	**PBV group**	**NPBV group**
Severe PS	18	6	12
Moderate PS	2	1	1
RCHF	2	1	1

with moderate PS in the PBV group were treated with the beta-blocker atenolol after diagnosis (0.5-1.0 mg/kg orally every 12 hours). In these patients, atenolol was known to be given until the last moment of follow-up or until death.

Fifteen dogs revisited the clinic for a free echocardiologic exam. The time between the previous visit and the new examination varied between 1 and 10 years. In 2 dogs the severity has changed from moderate to severe, where time between the previous check and the new examination was 1.5 and 3.5 years. The DG changed from 57 and 68 mmHg to 120 and 130 mmHg, respectively. In one dog, the DG remained severe but almost doubled from 109 to 208 mmHg in 5 years. In another dog, the DG changed from 33 to 53 mmHg 7¾ years after PBV.

Kaplan-Meier analysis and survival

Cardiac-related death occurred in 20 dogs (17.9%). In the PBV group, 7 dogs (6.3%) died, of which 6 dogs (5.4%) had severe PS and 1 dog (0.9%) had moderate PS. In the NPBV group, 13 dogs (11.6%) died, of which 12 dogs (10.7%) had severe PS and 1 dog (0.9%) had moderate PS (**Table 3**). Eleven dogs died for a non-cardiac reason. Of the dogs undergoing PBV, 2 dogs (3.1%) died during the procedure due to ventricular fibrillation and asystole. Both dogs had a DG >190 mmHg. One dog had type A PS and presented RCHF, the

Table 4. Survival in overall population, severe PS group, PBV group and NPBV group						
Survival: severe and moderate PS	**PBV (%)**	**NPBV (%)**	**Clinical signs (%)**	**No clinical signs (%)**	**TR (%)**	**No TR (%)**
1 year	96.8	91.0	84.9	97.4	85.6	96.4
2 years	96.8	85.7	74.9	97.4	73.7	96.4
3 years	96.8	75.2	74.9	91.6	73.7	91.3
4 years	93.7	67.6	69.5	86.6	52.7	89.2
Survival: severe PS	**PBV (%)**	**NPBV (%)**	**Clinical signs (%)**	**No clinical signs (%)**	**TR (%)**	**No TR (%)**
1 year	96.4	87.9	82.8	96.7	85.2	95.4
2 years	96.4	81.1	71.7	94.6	73.4	95.4
3 years	96.4	68.3	71.7	90.2	73.4	89.5
4 years	93.1	59.2	65.7	84.6	52.4	87.1
Survival: PBV	**Type A (%)**	**Type B (%)**	**Type inter-mediate (%)**			
1 year	97.8	88.9	100			
2 years	97.8	88.9	100			
3 years	97.8	88.9	100			
4 years	97.8	74.1				
Survival: NPBV	**Clinical signs (%)**	**No clinical signs (%)**				
1 year	78.8	96.6				
2 years	60.8	96.6				
3 years	60.8	80.7				
4 years	50.6	74.9				

Table 5. Univariate analysis in categories analyzed (significant results)		
Predictors	**Hazard ratio (95% CI)**	**P-value**
Severe and moderate PS		
Doppler gradient (any increase of 1 mmHg)	1.012 (1.001-1.023)	P=0.032
Age at diagnosis (any increase of 1 month)	1.020 (1.001-1.039)	P=0.027
Clinical signs	2.546 (1.053-6.156)	P=0.031
TR	3.579 (1.388-9.231)	P=0.005
PBV	0.339 (0.135-0.854)	P=0.016
Severe PS		
Doppler gradient (any increase of 1 mmHg)	1.013 (1.001-1.026)	P=0.035
Age at diagnosis (any increase of 1 month)	1.020 (1.002-1.039)	P=0.023
Clinical signs	2.494 (0.983-6.329)	P=0.046
TR	3.167 (1.206-8.313)	P=0.014
PBV	0.266 (0.099-0.710)	P=0.005
PBV group		
Doppler gradient (any increase of 1 mmHg)	1.022 (1.001-1.043)	P=0.029
Age at diagnosis (any increase of 1 month)	1.033 (1.006-1.061)	P=0.006
Valve morphology type B	7.026 (1.268-38.928)	P=0.025
Atenolol	6.349 (1.198-33.641)	P=0.014
NPBV group		
Clinical signs	3.287 (1.095-9.867)	P=0.025

other dog had an intermediate type and showed mild tricuspid regurgitation.

The Kaplan-Meier curves (**Figures 1 to 8**) show the significant outcomes (P<0.05) gained from the survival analysis. **Figures 1 to 3** show the effect of PBV, the effect of clinical signs and the effect of TR on the overall population. **Figures 4 to 6** show the same effects, but in the group of dogs with severe PS. **Figure 7** shows the effect of valve morphology in the PBV group, where dogs with type B have a significant shorter survival time. **Figure 8** shows the effect of clinical signs in the NPBV group.

Overall, the calculated one-year survival reached 94.2%. The calculated two-year survival was 91.8%, three-year survival 87.5% and four-year survival 82.4%. In the severe PS group the calculated one-year survival is 93.0%, two-year survival 90.2%, three-year survival 85.4% and four-year survival 79.6%. **Table 4** shows one to four-year survival in the groups with significant outcomes in the survival analysis.

The significant results of the univariate Cox proportional hazard analysis are shown in **Table 5**. Any increase of 1 mmHg (DG at the time of diagnosis) and any increase in 1 month of age (age at the time of diagnosis) is a risk factor for cardiac-related death in most groups analyzed. In the PBV group the use of atenolol shows a significant result, as patients with atenolol have a shorter survival time compared to dogs without atenolol. The calculated three-year survival of dogs with atenolol is 100% and in dogs without atenolol 96.2%, but five and seven-year survival in dogs with atenolol is 72.7% and 53%, respectively. In dogs without atenolol survival remains 96.2%.

The significant outcomes of the multivariate Cox proportional hazard analysis are displayed in **Table 6**. Any increase of 1 mmHg (DG at the time of diagnosis)

Table 6. Multivariate analysis in categories analyzed (significant results)		
Predictors	**Hazard ratio (95% CI)**	**P-value**
Severe and moderate PS		
Doppler gradient (any increase of 1 mmHg)	1.013 (1.002-1.024)	P=0.024
PBV	0.361 (0.129-1.014)	P=0.047
Severe PS		
Doppler gradient (any increase of 1 mmHg)	1.014 (1.002-1.028)	P=0.034
PBV	0.269 (0.092-0.782)	P=0.011
PBV group		
Atenolol	8.927 (1.102-72.331)	P=0.023
NPBV group		
Doppler gradient (any increase of 1 mmHg)	1.019 (1.003-1.035)	P=0.021

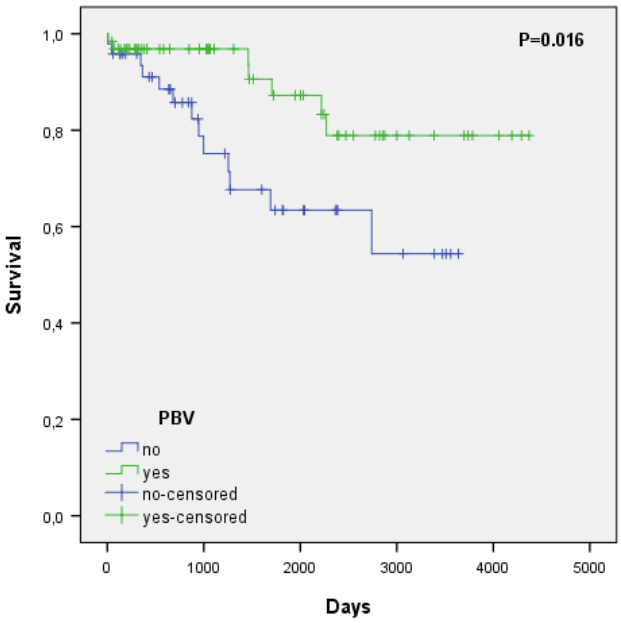

Figure 1. Kaplan-Meier survival curve in the overall population: a different survival time was observed in dogs undergoing PBV versus dogs not undergoing PBV. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

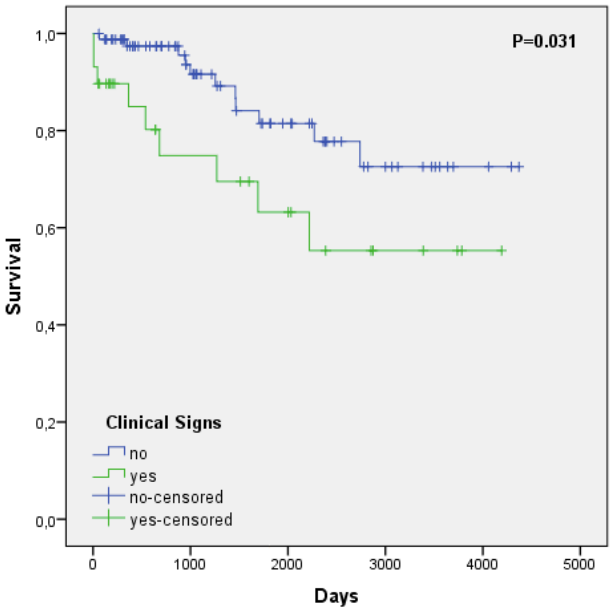

Figure 2. Kaplan-Meier survival curve in the overall population: a different survival time was observed in dogs with clinical signs versus dogs without clinical signs. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

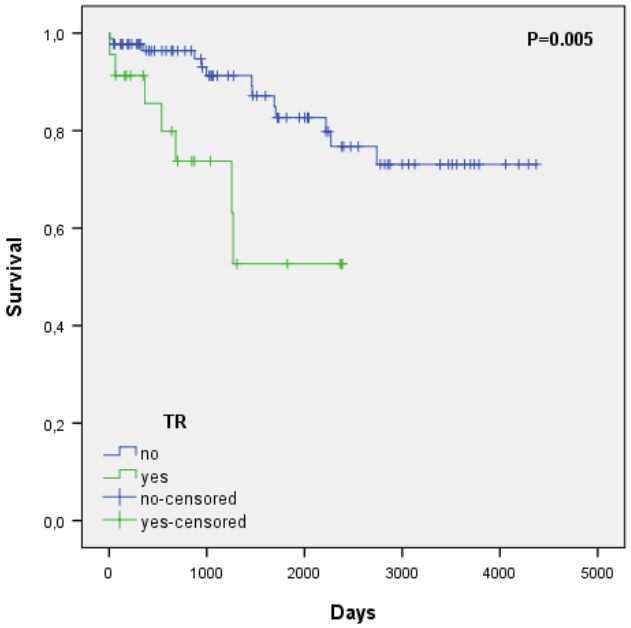

Figure 3. Kaplan-Meier survival curve in the overall population: a different survival time was observed in dogs with TR versus dogs without TR. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

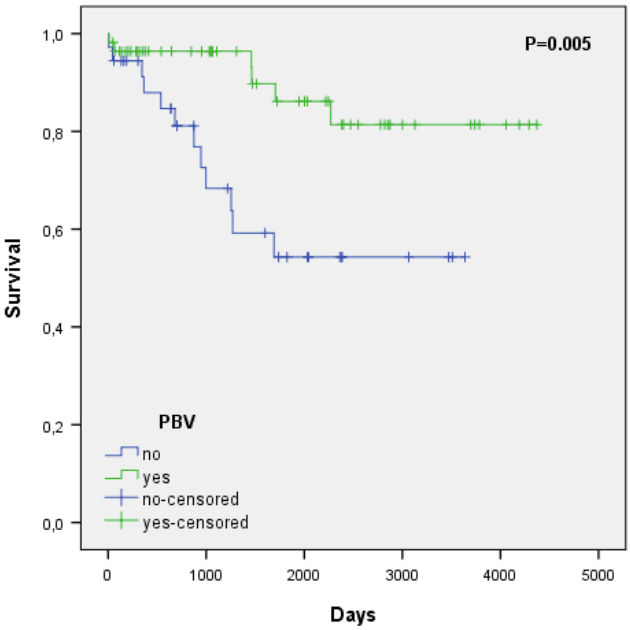

Figure 4. Kaplan-Meier survival curve in dogs with severe PS: a different survival time was observed in dogs undergoing PBV versus dogs not undergoing PBV. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

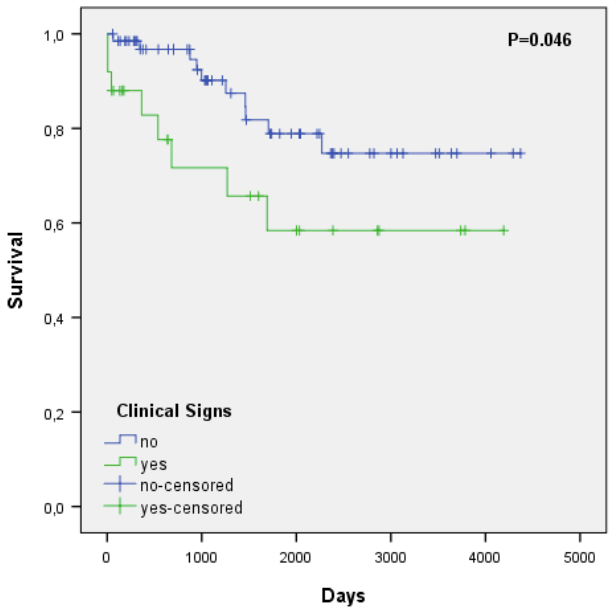

Figure 5. Kaplan-Meier survival curve in dogs with severe PS: a different survival time was observed in dogs with clinical signs versus dogs without clinical signs. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

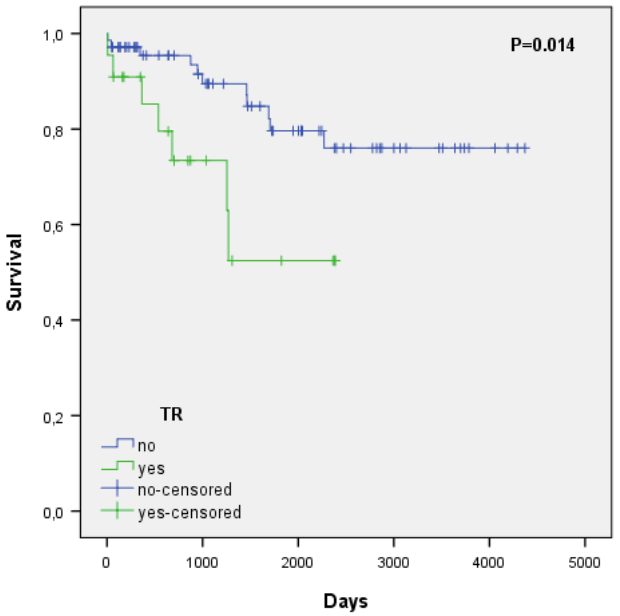

Figure 6. Kaplan-Meier survival curve in dogs with severe PS: a different survival time was observed in dogs with TR versus dogs without TR. Less than 50% of the dogs reached the final endpoint, thus median survival was not possible to be determined.

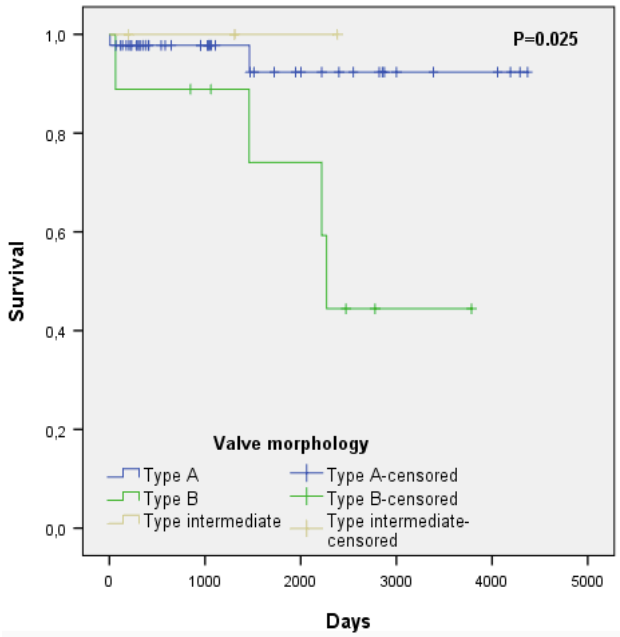

Figure 7. Kaplan-Meier survival curve in the PBV group: a different survival time was observed in dogs with type B (median survival time 2219 days) versus dogs with type A and the intermediate type. Less than 50% of the dogs with type A and the intermediate type reached the final endpoint, thus median survival was not possible to be determined.

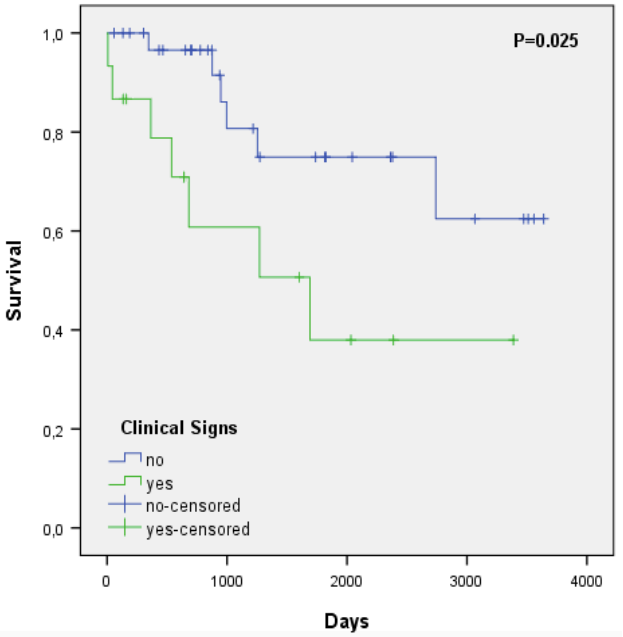

Figure 8. Kaplan-Meier survival curve in the NPBV group: a different survival time was observed in dogs with clinical signs (median survival time 641 days) versus dogs without clinical signs. Less than 50% of the dogs without clinical signs reached the final endpoint, thus median survival was not possible to be determined.

remains as a risk factor for cardiac-related death in the overall population, as well as in the severe PS group and in the NPBV group. PBV is a positive predictive factor in the overall population and in the severe PS group. In the PBV group, atenolol still is a negative predictive factor.

For analysis of the overall population and the severe PS group type B1 and B2 were first analyzed as separate types and then together as one type. The results of the analyses shown here have been done with type B1 and B2 as separate types, but analyses with these types combined have also been done and showed no differences.

Discussion

This study has been performed for the reason that only few other studies have analyzed survival and long-term predictors affecting survival in dogs with PS on which many veterinary clinics now base their decisions. Most studies included only severe PS. Only one study analyzed survival in both moderate and severe PS.[4] The dog population used in that study were all selected from the same center in one country. This means that there might have been a regional difference in dog breeds and therefore dissimilar DG and frequencies of valve morphologies when compared to other regions. Also, the cardiologists performing PBV might differ in success rates from other clinics. When comparing the results of this study and the study of Locatelli et al., there are many similarities. However, there are a few differences as well.

When analyzing the most common breeds in this study, breeds like the French Bulldog and Boxer dog have previously been described in other studies regarding PS.[1, 2, 4] However, no other studies have described a high frequency of PS in Rhodesian Ridgebacks and Nova Scotia Duck Tolling Retrievers. In Rhodesian Ridgebacks only type A PS has been identified. This might imply that in this breed only type A PS develops.

It has previously been described that Boxer dogs and French Bulldogs account for a large part of the type B PS population (70%).[4] In a recent study on French Bulldogs with PS, 60% of the bulldogs were diagnosed with type B PS.[19] This suggests that type B PS is more common in this dog breed. In this study, French Bulldogs are also overrepresented and account for 61% of the type B population. However, no Boxer dogs with type B PS were seen in this study. Only 5 Boxers were included in this study, so this might not represent the whole Boxer population and could explain why no Boxers with type B were seen.

In the survival curves and univariate analyses of the overall population and of the severe PS group, PBV, the presence of clinical signs and TR show significant results. Also in the NPBV group, clinical signs show a significant result. Dogs undergoing PBV show a longer survival time compared to dogs not undergoing PBV, a result that is comparable to results of other studies.[4, 8] Dogs showing clinical signs at the time of diagnosis and dogs with TR at the time of diagnosis show a shorter survival time than animals without clinical signs or TR. In the study of Locatelli et al. clinical signs were found significant as well, but TR was not found significant in either groups.[4] It has however been shown by others that TR is a risk factor, so the result of this study does compare to earlier results of these other studies.[8, 11] Valve morphology and age at time of diagnosis showed significant results in the study of Locatelli et al. in the whole population of dogs. Dogs with type B PS and dogs <1 year of age had a shorter survival time.[4] These findings are not comparable with the results in this study, where no significant results were found regarding type in the overall population and age <1 year at diagnosis. Only in the PBV group a significant shorter survival time can be seen in dogs with type B PS in the survival analysis, but this result has not been shown by Locatelli et al. An explanation for this result could be the more rigid and thick morphology of the valves and the presence of annulus hypoplasia. These characteristics might make PBV less successful, as the valves are harder to tear open and the annulus cannot be widened by PBV. In humans it is known that dysplastic PS (type B PS in dogs) may show suboptimal results after PBV with a higher frequency of restenosis.[20, 21] In this study in the univariate analysis age at diagnosis (any increase of 1 month of age) has been shown to be a negative predictor regarding survival. This is in conflict with the outcome of Locatelli et al., where diagnosis <1 year of age has been shown to be a risk factor. In another study on French Bulldogs, age at diagnosis (per 1 year increase) has however been shown to be a risk factor.[19]

Early diagnosis of PS might be beneficial for dogs with PS, as age seems to be a negative predictor of survival. Clinical signs and TR are also risk factors for cardiac-related death. If PS is recognized early, less secondary changes in the heart might have developed. Clinical signs and TR are less likely to have developed yet and early intervention can be performed. PBV will be likely to create a longer life span in these dogs.

In the multivariate analysis the pulmonary DG (any increase of 1 mmHg) is a risk factor for cardiac-related death in all groups except the PBV group. Pulmonary DG has been reported as a risk factor before, also by Locatelli et al.[4, 8, 11, 13] The DG not being a risk factor in the PBV group can easily be explained, as the DG should have been decreased by the treatment and survival is

proven to be significantly longer in these dogs in this study and by Locatelli et al.[4] Also in the multivariate analysis PBV is shown to be a positive predictive factor in the whole population of dogs and in the severe PS group, which corresponds with a lower risk for cardiac-related death. In the same groups in the study of Locatelli et al. no PBV is shown to be a negative predictor.[4] This is comparable to the positive predictive effect of PBV in this study.

In the study of Locatelli et al. the group of dogs with RCHF have been analyzed separately and RCHF has been analyzed as a risk factor in the survival curves.[4] In this study only 2 dogs presented with RCHF, so this analysis could not be performed. Both dogs however died of RCHF due to PS.

The results of the severe PS group are similar to the results of the overall population. This could be explained by the fact that 82% of the total population of dogs consists of dogs with severe PS and therefore make up a major part of the whole population. Only 18% of all patients have moderate PS (n=20). This number of dogs was too small to perform statistical analysis on. For this reason, no outcomes could be given on survival and risk factors in dogs with moderate PS. Recommendations regarding dogs with moderate PS are not yet clear. Locatelli et al. did not show a significant increase of survival time in dogs with moderate PS that underwent PBV.[4] However, in patients with moderate PS that show clinical signs PBV is generally recommended.[3] More studies with a larger number of dogs with moderate PS are needed to confirm this recommendation.

Even if it would have been possible to analyze the group of dogs with moderate PS, the results might not have perfectly represented all dogs with moderate PS. Dogs with moderate PS in the PBV group were all diagnosed with a DG of 60-70 mmHg or higher. Dogs with a lower moderate DG were therefore not represented in this group. Again, more studies on dogs with moderate PS that undergo PBV are needed.

Recommendations regarding dogs with severe PS are more clear, as PBV is considered the treatment of choice.[4, 8, 13] This study confirms earlier results of PBV in patients with severe PS. Survival in patients undergoing PBV is increased, as these dogs have a lower risk of cardiac-related death. PBV is however a treatment with risks, as the death rate was 3.1% in this study. This must be taken into consideration when discussing the options with the owners.

The administration of the beta-blocker atenolol in some dogs might have influenced the outcome of this study. However, no significant results were seen when comparing dogs receiving atenolol with dogs without atenolol. To exclude the effect of PBV, another analysis has been done in the NPBV population only, also comparing dogs receiving atenolol with dogs without atenolol. No significant difference has been seen here either. These outcomes indicate that atenolol did not influence the results of the survival in dogs without PBV. However, the multivariate analysis of dogs with PBV shows that atenolol is a negative predictive factor. This can be explained when looking into the group of PBV dogs that received atenolol. All these dogs did not have a very successful outcome after PBV and therefore received atenolol. The fact that success of PBV was minimal in these dogs (e.g. DG was still too high) explains why survival in these dogs is shorter compared to dogs without atenolol which had a more successful outcome after PBV.

A higher DG is regarded as a negative predictor of survival in dogs with PS, but in this study a few dogs with severe PS in the NPBV group have shown that it is possible to have a long survival period without clinical signs. Time between diagnosis and contact with the owner varied between 6.5 to 10 years. In this period these dogs lived a normal life without any clinical signs. This shows that severe PS does not always have a poor prognosis. However, in most dogs a high DG will still be a risk factor for cardiac-related death.

It has been noticed that in a couple of dogs that revisited the clinic for this study the DG has changed from moderate to severe when compared to the last echocardiographic check. This implies that the DG may still change after a couple of years and that it might be necessary to recheck dogs with PS at one year of age or even older. More studies are needed to confirm this speculation.

This study had some limitations due to its retrospective nature. Some echocardiographic data were not complete or not assessed as well as it would be nowadays. The type of PS was often not mentioned and not all echocardiographic images were present or of good quality. Therefore not all patients could be categorized into certain types of PS. To be able to calculate the aortic/pulmonary ratio the aortic and pulmonic annulus diameters are needed. However, in a few patients the diameters were not mentioned in the records and it was not possible to measure these in the echocardiographic images. In those patients it was assumed that it was of a certain type when the report explicitly described the presence of annulus hypoplasia or not and/or the presence of thickened leaflets or not. If this was not mentioned in the report, it was classified as type unknown. It might still be possible that if the images would have been present and measurements could have been done, that these patients might have been given another type. Also, assessment of the presence and severity of TR could not always be performed that well. Again, not all echocardiographic

images and records were complete and in some images it was not very reliable to measure the severity of TR. This means that some dogs with TR might have been categorized into another severity of TR or that in dogs without TR the TR might have been missed. Furthermore, owners could have misinterpreted clinical signs or failed to recognize cardiac-related death, which could have biased the results.

In conclusion, several risk factors have been identified. Pulmonary DG, age at the time of diagnosis, the presence of clinical signs and the presence of TR are risk factors for cardiac-related death in dogs with severe PS. Valve morphology type B is a negative prognostic indicator in dogs undergoing PBV. PBV is confirmed to prolong survival in dogs with severe PS and is therefore the elective treatment in these patients.

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