Restenosis After Balloon Valvuloplasty in Dogs with Congenital Pulmonary Stenosis

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This study was performed at Laboratory of Surgery 1, Azabu University and Azabu University Veterinary Teaching Hospital.

KEY WORDS: Pulmonary valve stenosis, Long-term follow-up, Atenolol

ABSTRACT

The aims of this study were to reveal the prevalence of complications associated with PBV over a long-term follow-up, and to investigate the factors related to those complications, especially pulmonary restenosis. Forty dogs who underwent PBV were retrospectively reviewed. Long-term follow-up was available in 22 dogs. Exacerbation of PI and TR after PBV was observed in some dogs; however, right-sided heart failure due to PI or TR was not observed in any of them. During long-term follow-up, restenosis developed in 6 dogs (6/22). Restenosis was noticed 5.5 months (ranging from 1.5 to 68.2 months) after successful PBV. Multiple regression analysis identified atenolol administration prior to PBV as the independent predictor of restenosis during long-term follow-up. Further investigation is warranted to investigate the mechanism of restenosis and to determine a strategy to prevent complications.

INTRODUCTION

Pulmonary stenosis (PS) is one of the most common congenital heart defects (CHD) in dogs.[1] Pulmonary valvular stenosis (PVS) is the most common form of PS.[1, 2] When PS is severe, the patient may develop syncope, right-sided congestive heart failures, or sudden death.[3-6]

Pulmonary balloon valvuloplasty (PBV) has been known to be effective for valvular stenosis, and is considered the first-line treatment for severe PVS in humans and dogs.[4, 5, 7, 8] According to previous literature of human and dogs, complications of PBV after successful reduction of PG included restenosis of pulmonary valve, tricuspid valve regurgitation (TR), and pulmonary valve insufficiency (PI). [3-5, 9-12] Restenosis was noticed in some patients during long-term follow-up after PBV despite decreasing of the peak instantaneous pressure gradient across the pulmonary valve (PG) at immediate follow-up after PBV.[3-5,9,10] To the best of author's knowledge, there has been no report in veterinary medicine focusing on the

complications of PBV, especially restenosis, during long-term follow-up.

The aims of this study were to reveal the prevalence of PBV complications in long-term follow-up, and to investigate the factors related to the complications, especially pulmonary restenosis.

MATERIALS AND METHODS

Medical records of dogs referred to Azabu University Veterinary Teaching Hospital Cardiology Service from September 2006 to October 2013 were retrospectively reviewed. Dogs who underwent successful PBV due to severe PVS, and whose long-term follow-up was available, were included in the study. A diagnosis of PVS was established by physical examination, thoracic radiography and echocardiography. Dogs with concurrent heart disease that was not hemodynamically significant were included, but dogs with hemodynamically significant concurrent heart disease were excluded from the study. The outcome acquired within one month after PBV was defined as the short-term follow-up.

Severity and localization of stenosis were evaluated using echocardiography before PBV. All echocardiographic images were acquired using ultrasound unit equipped with 4, 7, and 10 MHz transducers (Vivid 7 dimension, GE Medical System). Pulmonic blood flow velocity was assessed by continuous-wave Doppler using the right parasternal short axis +/- left cranial parasternal views, and higher velocity was used to calculate PG by modified Bernoulli equation. Severe PVS was diagnosed when PG was 80 mmHg or more. Severity of PI was classified as mild, moderate or severe according to the degree of the regurgitant jet filling the right ventricle: the jet extending only into the outflow tract was ”mild,” the jet proceeding to the tricuspid valve was ”severe,” and somewhere between the two was ”moderate.”[10] TR severity was assessed by color Doppler jet area to the right atrial area ratio:

- mild, less than 20%
- moderate, 20% to 50%
- severe, greater than 50%.[13]

The interventional procedures were performed under general anesthesia maintained with isoflurane and fentanyl (10-20 microgram/kg/hr, continuous rate infusion). The jugular vein was surgically exposed in left lateral recumbency, and a catheter introducer was inserted. When the jugular vein was hypoplastic, the femoral vein was used for vascular access instead. After measuring the right ventricular and pulmonary artery pressures using multipurpose catheter, the pulmonary annulus diameter was measured by performing right ventricular angiography. The diameter of the balloon catheter (TYSHAK NuMed, USA) was selected based on it being approximately 1.2 times the diameter of the pulmonary artery annulus. Successful inflation was achieved when a loss of the waist was visualized during balloon inflation. When ventricular arrhythmia was observed during the procedure, lidocaine was administered. PG was again assessed by measuring the peak pulmonary artery and right ventricle pressure after inflation, to confirm the effectiveness of the procedure.

Echocardiography was repeated after PBV at various times for each case. If PG decreased below 80 mmHg after PBV, the procedure was considered successful. Restenosis was defined as PG decreasing below 80 mmHg after PBV, but increasing to 80 mmHg or more, as observed during long-term follow-up.[2] Dogs were divided into two groups on the basis of presence of restenosis; the success group and restenosis group.

Statistical analysis was performed with the statistical package for Ekuseru-Toukei 2010. Results were expressed as mean ± standard deviation. The comparison of PG between pre and post PBV at short-term follow-up was performed by Wilcoxon signed-rank test. The comparison of variables between the success group and the restenosis group was performed by Mann-Whitney U test. In order to examine the factors associated with restenosis, multiple

Table 1: *Characteristics and clinical findings of 38 dogs who underwent PBV.*

Variables	All dogs (n = 38)	The dogs whom long-term follow-up was available (n = 22)	P value
Sex (male/female)	21/17	11/11	
Age (months)	19.6±27.1 (3.3-127.7)	25.4±33.7 (3.3-12.77)	0.72
Weight (kg)	5.4±27.1 (1.6-18.9)	6.3±4.6 (1.8-18.9)	0.53
Pre-PBV PG (mmHg)	138.5±50.7 (80.9-267.9)	149.8±59.2 (80.9-267.9)	0.61
Short-term follow-up PG (mmHg)	42.7±14.4 (16.1-74.94)	43.7±15.8 (16.1-74.9)	0.75
Numbers of balloon inflation	3.8±1.9 (1-10)	3.8±1.6 (1-6)	0.67
BAR	1.4±0.2 (1.1-2.0)	1.4±0.2 (1.1-2.0)	0.89

PBV: Pulmonary balloon valvuloplasty, PG: The peak instantaneous pressure gradient across the pulmonary valve, BAR: Balloon annulus ratio

regression analysis was performed with the following variables:

- age (months) at the time of PBV
- weight (kg)
- PG prior to PBV
- PG at short-term follow-up
- the number of balloon inflations
- Balloon Annulus Rate (BAR)
- concurrent congenital heart disease
- atenolol administration prior to PBV, and
- candesartan administration prior to PBV.

A difference with $P < 0.05$ was considered significant.

RESULTS

A total of 40 dogs underwent PBV during the study period. Two cases were unsuccessful and excluded from the study--one of them died during the procedure due to perforation of pulmonary artery, and the other did not achieve relief of stenosis. Therefore, the immediate success rate was 95% (38/40). The characteristics and clinical features of cases were summarized in Table 1. The mean PG of 38 dogs prior to PBV was 138.5 mmHg. PG was significantly decreased to 42.7 mmHg postoperatively ($P < 0.001$). The mean numbers of balloon inflations and the effective BAR were also shown in Table 1.

Although short-term follow-up was available for all dogs, long-term follow-up was available for 22 out of 38 dogs (Table 1). The median follow-up period was 37.8 months (ranging from 10.3 to 73.9 months). Fourteen different breeds were represented in this group of dogs. The common breeds included Chihuahua (n=5), mixed breed dogs (n=3), French bulldogs (n=2), and miniature pinschers (n=2). Concurrent hemodynamically irrelevant heart diseases were identified in 10 dogs (one dog had two heart diseases in addition to PVS):

- five had PFO with right-to-left shunt
- two had a left persistent cranial vena cava
- two had ventricular septal defect (one; left-to-right, one; right-to-left), and
- one had mild subaortic stenosis.

In 22 dogs for whom long-term follow-up was available, there was a significant reduction in mean PG from 149.8 mmHg (ranging from 80.9 to 267.9 mmHg) to 43.7 mmHg (range 16.1 to 74.9 mmHg) after PBV ($P < 0.001$) at short-term follow-up. Restenosis was observed in 6 out of 22 dogs

Table 2: *Characteristics and clinical findings of success group and restenosis group.*

Variables	Success group (n = 16)	Restenosis group (n = 6)	P value
Sex (male/female)	6/10	5/1	
Age (months)	27.8±36.9 (4.0-127.7)	18.9±25.0 (3.3-68.8)	0.66
Weight (kg)	5.4±3.7 (1.8-13.1)	8.6± 6.3 (2.5-18.9)	0.24
Pre-PBV PG (mmHg)	148.1±61.8 (80.9-267.9)	154.4±56.8 (90.8-245.2)	0.83
PG in short-term follow-up (mmHg)	39.3 (16.1-66.1)	52.2±14.7 (41.8-74.9)	0.10
Numbers of balloon inflation	3.3±1.5 (1.0-6.0)	4.3±1.6 (2.0-6.0)	0.16
BAR	1.4±0.2 (1.1-1.8)	1.4±0.3 (1.3-2.0)	0.18

PBV: Pulmonary balloon valvuloplasty, PG: The peak instantaneous pressure gradient across the pulmonary valve, BAR: Balloon annulus ratio

during long-term follow-up (Table 2). The median time when restenosis was revealed was 5.5 months (ranging from 1.5 to 68.2 months) after PBV. Changes of PG in each dog of the restenosis group were shown in Fig 1.

All dogs were prescribed one or more medications before PBV. Fourteen dogs were on beta-blockers (atenolol: 11 dogs in success group and 2 dogs in restenosis group, carvedilol: 1 dog in success group), 13 dogs were on candesartan (10 dogs in success group and 3 dogs in restenosis group), and 1 dog was on enalapril. Multiple regression analysis identified atenolol administration prior to PBV as the independent predictors of restenosis during long-term follow-up (Table 3). Because all dogs except one were on atenolol and candesartan after PBV, medication after PBV was not included in multiple regression analysis.

Four out of 22 dogs were classified as having mild PI, seven dogs had moderate PI, and no dogs had severe PI before PBV. PI in four dogs worsened after PBV in short-term follow-up, although the severity of PI in two dogs was improved during long-term follow-up. TR was revealed in four dogs before PBV. Two of them had mild TR and the other two had severe TR. Although deterioration of TR severity was observed in 12 dogs at short-term follow-up, TR improved at long-term follow-up in 10 dogs. None of the dogs was considered to have severe TR at the latest follow-up. The right-sided heart failure due to PI and/or TR was not developed in any dogs during the observation period.

DISCUSSION

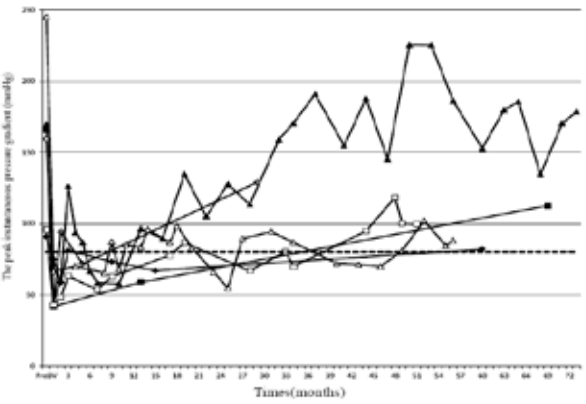
Previous studies reported that restenosis after PBV was noticed in long-term follow-up,[3-5,10] and that it progressed over time.[9,11,14] In the present study, 6 out of 22 dogs (27.3%) developed restenosis after successful PBV at medium to long-term follow-up (1.5 to 68.2 months). The incidence of restenosis in this study appeared to be about the same as those of previous veterinary reports (8-31%).[3-5, 10, 12]

Rao et al. demonstrated two risk factors for restenosis: BAR < 1.2 and immediate post valvuloplasty gradient > 30 mmHg.[15] No dogs in the restenosis group had BAR < 1.2 in our study. In addition, post PBV PG was not statistically different between the restenosis group and success group. Locatelli et al reported that BAR or PG post PBV did not seem to be related to the occurrence of restenosis either.[10]

Our present study revealed that beta-blocker administration prior to PBV was associated with incidence of restenosis. Beta

blockers have negative chronotropic and inotropic effects, which could possibly reduce the mechanical stress to the heart valve. Guo et al reported that the mechanical stretch to cardiac fibroblasts increased collagen and glycosaminoglycan in vitro.[16] A human pulmonary valve consists of endothelial cell, fibroblast, glycosaminoglycan, and collagen,[17] as in dogs (unpublished data from our laboratory). Although degeneration of the pulmonary valve after PBV was not pathohistologically investigated at this time, pathological changes due to mechanical stress could possibly be related to restenosis. Reduction of mechanical stress could be one of the strategies for preventing restenosis, although a prospective study is needed. Additionally, Ohlstein et al reported that carvedilol afforded superb profound protection against balloon angioplasty-induced neointimal smooth muscle cell proliferation, migration, and vascular stenosis in an animal model.[18]

Figure 1: *The changes of peak instantaneous pressure gradient across the pulmonary valve (mmHg) during long-term follow-up in 6 dogs who developed restenosis. Dotted line shows 80 mmHg.*



Kim et al reported that a carvedilol-coated stent inhibited neointimal hyperplasia in a porcine stent restenosis model.[19] On the other hand, sustained oral administration of carvedilol and atenolol was not effective for reducing stent restenosis in a human patient,[20] although their target vessel and types of vascular injury were very different from those of our dogs. Further investigation is warranted to determine the effect of beta blockers on prevention of restenosis in dogs after PBV.

Exacerbation of PI and TR was observed in some dogs after PBV; however, right-sided heart failure due to PI or TR was not observed in any of our dogs. The same tendency was observed in previous veterinary studies as well.[5, 10] In human patients,

Table 3: *Results of multiple regression analysis.*

Variables	95% Confidence interval	P value
Age (months)	-0.002 to 0.010	0.16
Weight (kg)	-0.071 to 0.053	0.77
Pre-PBV PG (mmHg)	-0.001 to 0.007	0.19
Short-term follow-up PG (mmHg)	-0.017 to 0.017	1.00
Numbers of balloon inflation	-0.283 to 0.029	0.10
Balloon annulus ratio (BAR)	-1.458 to 0.361	0.22
Pre-PBV beta-blocker	0.172 to 1.071	0.01
Pre-PBV candesartan	-0.145 to 0.941	0.14

PBV: Pulmonary balloon valvuloplasty, PG: The peak instantaneous pressure gradient across the pulmonary valve, BAR: Balloon annulus ratio

prevalence of right-sided heart failure due to PI was reportedly low among those who underwent PBV compared with those who underwent surgery.[9, 11] It was suggested that PI was related to a large BAR, and that the severity of PI was associated also with the dysfunction of the right ventricule.[21] Selection of an appropriate balloon size on the basis of accurate measurement of pulmonary artery annulus is required in order to prevent right-sided congestive heart failure. Romeih et al reported that a patient with moderate pulmonary restenosis after relief of severe PVS showed more severe right ventricular dysfunction than a patient with moderate native PS.[22] Although none of our patients developed heart failure in this study, dogs with restenosis and valvular regurgitation should be considered high-risk patients to develop heart failure.

Limitations to this study were primarily associated with its retrospective nature. The number of dogs at long-term follow-up was small, and this could have influenced our results.

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