

Effect of preoperative administration of atenolol to dogs with pulmonic stenosis undergoing interventional procedures

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Abstract

Background: Beta-blockade is sometimes used in dogs with pulmonic stenosis with the intent of reducing frequency of ventricular arrhythmias during right heart catheterization.

Objectives: To evaluate if pretreatment with atenolol reduces frequency of ventricular arrhythmias, anesthetist interventions, or shortens procedure time.

Animals: Thirty dogs with pulmonic stenosis scheduled for interventional procedures.

Methods: Single center, prospective, randomized, open-label study. Dogs were randomized to treatment with atenolol or no treatment preoperatively for a minimum of 10 days. Variables recorded included heart rate, arrhythmias and complexity, total procedure time and administration of antiarrhythmic treatment, vasopressors, positive chronotropes, or fluid boluses.

Results: Fifteen dogs were enrolled in each group. Dogs receiving atenolol had lower mean heart rates during the procedure (atenolol 100 ± 11 bpm vs untreated 115 ± 19 bpm, $P = .01$). There were no significant differences between the atenolol and untreated groups in the frequency of ventricular ectopic complexes (535 [6-5296] vs 553 [79-2863], $P = .9$), ventricular couplets (46 [0-481] vs 29 [3-121], $P = .59$), ventricular triplets (20 [0-265] vs 16 [1-82], $P = .67$), ventricular tachycardia (8 [0-224] vs 8 [1-118], $P = .99$), proportion exhibiting R-on-T phenomenon (11/15 vs 14/15, $P = .33$), proportion receiving intraoperative lidocaine (1/15 vs 3/15, $P = .6$), vasopressors/positive chronotropes (11/15 vs 5/15, $P = .06$), or fluid boluses (12/15 vs 7/15, $P = .13$). The procedure time was similar (atenolol 41 [23-68] min vs untreated 35 [18-98] min, $P = .91$).

Conclusions and Clinical Importance: No benefit of preoperative atenolol treatment was identified in this small group of dogs.

KEYWORDS

balloon valvuloplasty, beta-blockers, intravascular stent, pulmonic stenosis

Abbreviations: CRI, continuous rate infusion; cTnI, cardiac troponin-I; PS, pulmonic stenosis; SVPC, supraventricular premature complex; SVT, supraventricular tachycardia; VPC, ventricular premature complexes; VT, ventricular tachycardia; VTI, velocity time integral.

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1 | INTRODUCTION

Pulmonic stenosis (PS) is 1 of the most commonly diagnosed congenital heart diseases in dogs.¹⁻⁵ Increased pressure during systole must be generated by the right ventricle to overcome the stenosis, which results in right ventricular hypertrophy and dilatation in severely affected dogs. Clinical signs of exercise intolerance, weakness or collapse might result, associated with poor cardiac output or hypotension, respectively, the latter most likely to be related to a vasodepressor reflex triggered by activation of ventricular mechanoreceptors or ventricular tachyarrhythmias caused by ischemic damage.⁶ Some dogs will eventually develop right-sided congestive failure or sudden death.^{7,8} The recommended treatment for dogs with severe PS is pulmonic balloon valvuloplasty, which is associated with improved survival time for dogs with valve leaflet fusion (type A PS).⁸⁻¹⁰ Balloon valvuloplasty might be less successful in cases with severely dysplastic valves, with or without hypoplasia of the pulmonary artery annulus⁸ in which cases transpulmonic stent might alleviate clinical signs.¹¹⁻¹³

During balloon valvuloplasty, catheterization of the right ventricular outflow tract is associated with ventricular arrhythmias in up to 87% of dogs¹⁴ and posing a risk of intraoperative hypotension or electrical instability, resulting in ventricular fibrillation. In human patients undergoing cardiac interventions, preoperative use of beta-blockers for a minimum of 7-days substantially reduces supraventricular and ventricular arrhythmias during the procedure.¹⁵ In addition to their antiarrhythmic properties, beta-blockers have a negative inotropic and chronotropic effect, reducing myocardial oxygen demand,¹⁶ which might reduce the risk of ischemic events. Additional benefits could arise from reduced heart rate or wall motion, which could potentially facilitate balloon or stent positioning. However, the same effects of beta-blockers might be detrimental under anesthesia, causing bradycardia in a dog that is heart rate dependent because of fixed stenosis, resulting in hypotension which could increase the need for anesthetist intervention during procedures.

In dogs, there are no published data, nor expert consensus, supporting the use of preoperative administration of beta-blockers in dogs undergoing catheterization of the right ventricle outflow tract.

The primary aim of this study was to determine whether treatment with atenolol for at least 10 days preoperatively would reduce the frequency of arrhythmias during balloon valvuloplasty or transpulmonic stent placement. The secondary aims of the study were to determine if¹: atenolol use was associated with reduced anesthetist intervention (use of antiarrhythmic drugs, vasopressors, positive chronotropes, or fluid boluses)²; atenolol use was associated with a reduced procedure time; and,³ atenolol use was associated with reduced ischemic damage evidenced by reduced serum cardiac troponin I (cTnI) measurements.

2 | MATERIAL AND METHODS

2.1 | Animals

This study was approved by institutional ethical review (VIN/18/016). Client-owned dogs with PS presenting to the University of Bristol

Veterinary Teaching Hospital, UK, were eligible for inclusion. Dogs scheduled to undergo balloon valvuloplasty or transpulmonic stent procedure were prospectively enrolled in the study after informed consent for study participation was obtained from the owner. Dogs were excluded if they had a disease that might cause arrhythmias (such as gastrointestinal disorders, splenic masses, adrenal, or urological diseases), or if they had a clinical suspicion of pulmonary hypertension. Concurrent congenital heart disease was not an exclusion criterion, but acquired heart disease would have led to exclusion.

2.2 | Study design

In this single center, open-label study, dogs were randomized to either receive atenolol (uptitrated over 10 days to a target dose of 1.5 to 2 mg/kg twice daily, given for a minimum of 3 days preoperatively) or no treatment. Dogs were scheduled to attend on 3 occasions: visit 1, before randomization; visit 2, for the interventional procedure; and visit 3, for 4-week follow-up after the operation. At visit 1, dogs underwent diagnostic echocardiography and measurement of serum cTnI. They were then randomized to either the treatment or the control group using a random number generator (<https://www.random.org>) and discharged from the hospital.

Visit 2 occurred a minimum of 10 days later, and consisted of repeat echocardiography and cTnI measurement, followed by cardiac intervention. At visit 2, owners were asked specific, standardized questions about any change in the dog's level of energy, exercise tolerance and appetite, in addition to the presence of signs of gastrointestinal disease, and episodes of weakness or collapse. All dogs were discharged the following day and returned for visit 3 approximately 4 weeks later. At this final visit, echocardiography and measurement of serum cTnI were repeated.

2.3 | Echocardiographic measurements and calculations

Standard echocardiographic views were obtained using a Vivid E95 (GE Health Care, Hatfield, UK) by a Board-certified veterinary cardiologist or a cardiology resident under direct supervision. Phased-array transducers were used (either 6S or 5S model).

Pulmonic stenosis morphology was classified as previously described into types A and B,⁸ based on aortic : pulmonary annulus diameter and the presence or absence of commissural fusion. If an intermediate form was identified, it was classified as type B if pulmonary annulus hypoplasia (aortic : pulmonary annulus diameter ratio >1.2) was present. Maximum pressure gradient across the pulmonic valve and pulmonic to aortic velocity time integral (VTI) ratio were both calculated. Aortic measurements were obtained from a subcostal view in all dogs, and pulmonic measurements were obtained from either a right parasternal short-axis view optimized for the main pulmonary artery, or a left cranial view optimized similarly. All measurements were performed by a single operator (SG) using a digital workstation (Echopac clinical workstation software, GE Health Care,

Hatfield, UK). This operator was blinded to the treatment group at the time of measurement. The continuous wave Doppler-derived profile of aortic and pulmonic flow were determined by tracing the outer edge of the modal velocities throughout systole.¹⁷ The software package calculated the VTI based on this data, and ratio was manually calculated. An average of 3 consecutive measurements was recorded for each variable. Severity of PS was defined according to veterinary guidelines; with a maximum pressure gradient of 50 to 80 mm Hg being moderate and a maximum pressure gradient ≥ 80 mm Hg considered as severe.¹⁸

2.4 | Interventional procedure

All interventions were performed by Board-certified veterinary cardiologists with residents under direct supervision. The choice of the procedure (balloon valvuloplasty vs transpulmonic stent) was based upon echocardiographic findings of pulmonary valve and arterial morphology. Transpulmonic stent angioplasty was recommended in the presence of supravalvular stenosis, pulmonary hypoplasia with vestigial valve leaflets identified obstructing the lumen, or where a coronary artery anomaly was detected which prevented standard balloon valvuloplasty being performed. Specific decisions regarding the type of equipment used were at the discretion of the attending clinician, although the procedure was generally performed as below.

Intervention was performed via the right jugular vein or right femoral vein as described.¹⁹ Briefly, a vascular introducer was placed in the access vessel. A catheter was advanced into the right ventricle and pressure measured. After this, a right ventriculogram using iodinated contrast material (Omnipaque 300 [647 mg of iohexol per mL, equivalent to 300 mg of organic iodine per mL], GE Health Care, Hatfield, UK) at the dose of 1.5 to 2 mL/kg was performed, including assessment of the levophase for coronary anatomy. The main pulmonary artery was catheterized and a rigid guidewire (Rosen wire 180 cm 0.035" Infiniti medical, Huddersfield, UK) situated in a branch pulmonary artery. Balloon choice (Veterinary Balloon catheter, Infinity Medical, Hopkinton, Massachusetts) was based on 1.3 to 1.5 \times annulus diameter.²⁰ In cases where a single balloon of greater than 18 mm would have been required, a double balloon procedure was performed, with effective orifice size calculation as previously described.²¹ All dilations were performed using a manual inflation device, to approximately burst pressure, and held for 3 to 5 seconds. Dogs underwent at least two balloon inflations, but further repeat inflations were performed in some cases.

Transpulmonic stent procedures were performed using a broadly similar technique, with a balloon expandable metallic stent as previously described.¹³ Right ventricular pressure was measured in all dogs after balloon inflations or stent deployment. In dogs with concurrent congenital heart disease, additional procedures were performed after the pulmonic balloon valvuloplasty, as described.²²⁻²⁴

2.5 | Cardiac troponin I measurements

Blood samples were collected into plain tubes, centrifuged at 1751 G for 5 minutes after formation of the blood clot, and analyzed within

24 hours of collection at a commercial laboratory. Serum cTnI concentration was measured using a 2-site immune enzymometric assay with a lower detection limit of 0.02 ng/mL, validated in dogs (ST AIA-PACK cTnI 3rd-Gen, Tosoh, Reading, UK). The upper limit of the reference range for dogs using this assay has been established as 0.1 ng/mL.

2.6 | Anesthesia

The preferred anesthetic protocol for this study was: premedication with methadone (0.3 mg/kg, IV); co-induction using midazolam (0.2 mg/kg, IV) followed by etomidate (to effect, IV); maintenance with sevoflurane (vaporizer setting, 1%-4% adjusted as needed). In some cases, an alternative anesthetic protocol was used, if it was decided to be in the best interest of the dog by the attending anesthetist. Administration of additional intervention was recorded—these included lidocaine boluses, lidocaine continuous rate infusion (CRI), other antiarrhythmic drugs, fluid boluses, and vasopressor or chronotropic agents.

2.7 | Perioperative ECG recording

In addition to standard cardiovascular monitoring, a Holter ECG monitor (Lifecard CF, Spacelabs Healthcare, Hertford, UK) was placed within 5 minutes of anesthesia induction. Dogs were positioned in left lateral recumbency if the right jugular approach was used, or right lateral recumbency if the right femoral approach was used. An ECG electrode was placed on the medial aspect of the elbow of the lower forelimb, the lateral aspect of the elbow of the upper forelimb, and the lateral aspect of the stifle of the upper hindlimb. The Holter was removed at least 2-hours after extubation. Holter analysis was performed by an external company (Express Diagnostics, Plymouth, UK—via HeartVets, UK). Data were analyzed between 2 time points: from initial cardiac intervention (pressure measurement or angiogram) to the removal of catheters and guidewires.

2.8 | Statistical analysis

Normality was assessed graphically and using a Shapiro Wilk test. Variables that were nonnormally distributed were expressed as median and range, and normally distributed variables were expressed as mean and SD. Categorical data were expressed as counts and percentages. Frequency data is presented as median (range). Fisher's exact test or chi-squared test were used to compare categorical data between groups. A Mann-Whitney *U* test was used to compare nonnormally distributed continuous data between 2 groups. A Wilcoxon-signed rank test was used to analyze paired data from sequential visits in the same dog. A prospective sample size analysis, extrapolating from meta-analysis of data in humans¹⁵ and 1 study in dogs,¹⁴ suggested that recruiting 15 individuals to each treatment group would have an 80% power to detect a difference in ventricular arrhythmias between

groups (<http://www.openepi.com>)—a Fleiss method with continuity correction was used. *P*-value less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Subject enrolment

Thirty-two dogs were initially enrolled in the study. Twenty-eight underwent randomization as described. Four dogs were referred for an interventional procedure after diagnosis of PS by another cardiologist. In these cases, only visits 2 (preoperative) and 3 (4-weeks after intervention) were recorded. Two of these dogs had been treated with atenolol for at least 10 days before presentation, and the other 2 had not been prescribed atenolol. These dogs were included in the corresponding group.

One dog was excluded from the study because the owner discontinued atenolol treatment a few days before the scheduled intervention. Another dog was excluded because dexmedetomidine was included in his anesthetic protocol, which could have affected the heart rate and rhythm. Thirty dogs were included in the study, featuring 21 breeds. French Bulldogs (*n* = 5), and Cavalier King Charles Spaniel (*n* = 3) were most commonly represented, with 1 individual each of 19 other breeds. Of the 30 dogs, 15 dogs were in the atenolol group and 15 dogs were in the untreated group.

Median age was similar in the untreated and atenolol groups: 5 months (2-96 months) and 6 months (2-20 months; *P* = .88) respectively. There was no difference in weight between groups (untreated 6.8 ± 4 kg vs atenolol 9.8 ± 5.7 kg; *P* = .11). There were more females represented in the untreated group; 12/15 (80%) vs 5/15 (33%) in the atenolol group (*P* = .02).

Additional concurrent congenital disorders are described in Table 1. There was no difference between groups in the proportion of dogs with concurrent congenital disorders (untreated 5/15 vs atenolol 6/15 dogs, *P* = 1). Type B PS was diagnosed in 5/15 untreated dogs and 2/15 dogs in the atenolol group (remainder were type A) (*P* = .39).

Defect	Atenolol	Untreated	Total
Isolated pulmonic stenosis (PS)	9	10	19
Tetralogy of Fallot	2	0	2
PS and patent <i>foramen ovale</i>	1	1	2
PS, patent <i>foramen ovale</i> and restrictive ventricular septal defect	1	0	1
PS and perimembranous ventricular septal defect	0	1	1
PS and valvular aortic stenosis	0	1	1
PS, <i>cor triatriatum dexter</i> and tricuspid dysplasia	0	1	1
PS and tricuspid dysplasia	1	0	1
PS and patent <i>ductus arteriosus</i>	1	0	1
PS and secundum-type atrial septal defect	0	1	1

3.2 | Clinical signs between visits 1 and 2

Clinical signs reported by the owners between the time of diagnosis (pretreatment, visit 1) and the day of admission for the procedure (visit 2, preoperative) were not significantly different between groups. A change in behavior between visits was reported in 0/15 (0%) untreated dogs and 4/15 (26%) dogs receiving atenolol (*P* = .1); 1 dog was more lethargic and 3 dogs were reported to be more energetic. An improved exercise tolerance was reported in 1/15 (6%) untreated dogs and 3/15 (20%) in the atenolol group (*P* = .6). Episodes of syncope between visits were reported in 1/15 (6%) untreated and no dogs on atenolol. Episodes of weakness were reported in no untreated dogs, and 1 dog receiving atenolol (6%) (*P* = 1). Change in appetite was reported in neither group (*P* = 1), and overt signs of gastrointestinal disease in only 1 dog receiving atenolol (6%) (*P* = 1).

3.3 | Cardiac intervention

Procedures performed were selected as required for individual dogs, but all comprised catheterization of the right ventricular outflow tract and balloon inflation across a stenotic lesion at the level of the valve (Table 2). In 3 dogs, additional procedures were performed under the same anesthetic (see Table 2 for details). There was no significant

TABLE 2 Procedures undergone by dogs enrolled in the study

Procedure performed	Atenolol	Untreated
Single balloon valvuloplasty	10	11
Double balloon valvuloplasty	3	1
Stent angioplasty and <i>cor triatriatum dexter</i> balloon	0	1
Balloon valvuloplasty and Amplatzer canine duct occluder	1	0
Pulmonic transvalvular stent angioplasty	1	1
Pulmonic transvalvular stent angioplasty and Amplatz atrial septal occluder	0	1
Total	15	15

TABLE 1 Number of dogs classified according to their congenital heart disease and group

difference in procedure time in the untreated and atenolol group (32 [18-58] minutes and 37.5 [23-68] minutes, respectively [$P = .73$]). For the purpose of this analyzing procedure time, cases that had another intervention in addition to stent or balloon valvuloplasty were removed from the analysis.

The number of balloon inflations was not different between groups: untreated dogs underwent a median of 2 inflations (range, 1-7) and dogs in the atenolol group underwent a median of 3 inflations (range, 1-7, $P = .47$).

Twenty-six dogs underwent the preferred anesthetic protocol, 2 dogs also received fentanyl in addition to the protocol, 2 dogs received alfaxalone as premedicating agents. These decisions were made at the discretion of the anesthetist. One dog, in the atenolol group, was placed on a CRI of esmolol at the beginning of the procedure, but the rationale for this variation in protocol was not recorded by the anesthetist. Six anesthetists were involved in the study, with 1 anesthetist performing 21 cases.

3.4 | Intraoperative ECG data

A significantly lower heart rate (minimum, mean, and maximum) was detected in dogs treated with atenolol compared to the untreated group

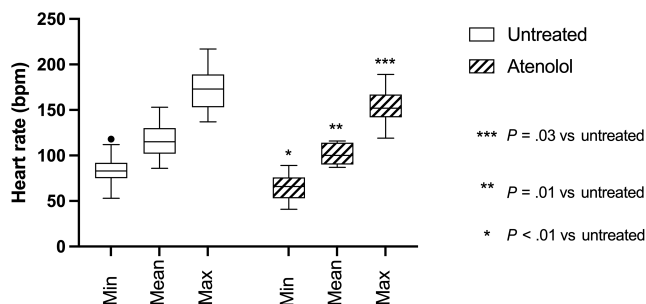


FIGURE 1 Minimum (min), mean and maximum (max) heart rates detected on Holter recordings. Dogs in the atenolol group measured lower for all variables than the untreated group

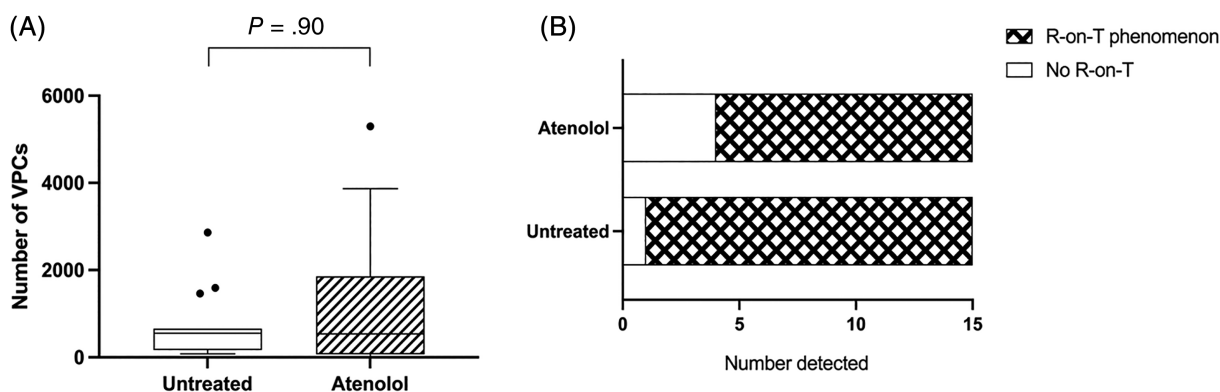


FIGURE 2 (A) The total number of ventricular premature complexes (VPCs) detected on an intraoperative Holter recording. There was no significant difference in frequency between treatment groups. (B) The number of dogs experiencing R-on-T phenomenon intraoperatively. There was no significant difference in frequency between groups

(Figure 1). There was no significant difference in the total number of ventricular premature complexes (Figure 2A), nor in the total numbers of couplets, triplets, salvos, ventricular tachycardia (VT) episodes, or maximum VT rate, longest VT run, number of supraventricular premature complexes or number of supraventricular tachycardia episodes (Table 3). Some dogs in both groups had R-on-T phenomenon, but there was no significant difference in the proportions affected (Figure 2B, $P = .33$).

3.5 | Requirement for anesthetist intervention

There were no significant differences between the 2 groups when any of the anesthetist interventions were monitored. In addition, no association between the presence of right-to-left shunts and a requirement for anesthetist intervention was detected ($P = .14$). A lidocaine bolus was deemed necessary and administered by the anesthetist in 3/15 untreated dogs and 1 atenolol-treated dog ($P = .6$). Similarly, there was no significant difference in the proportion of dogs receiving a constant rate infusion of lidocaine; 2/15 untreated dogs compared with none in the atenolol group ($P = .48$). Dogs in the atenolol group were treated for intraoperative hypotension (positive chronotropic or vasopressor drugs) in 11/15 cases, compared to 5/15 untreated dogs (Figure 3, $P = .07$). Fluid boluses were administered to 12/15 dogs in the atenolol group, compared to 7/15 untreated dogs ($P = .13$).

3.6 | Cardiac troponin I measurements

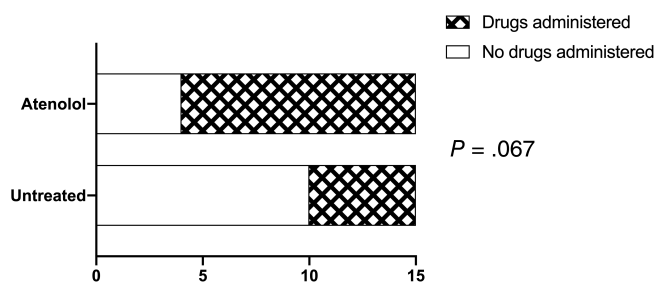
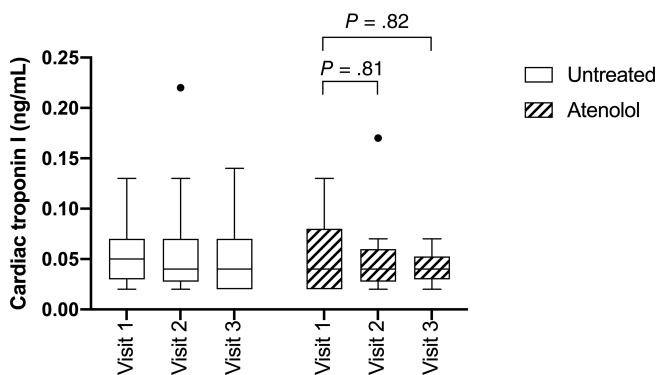
Twenty-three dogs had measurement of serum cTnI at visit 1, 28 had measurement of serum cTnI at visit 2 and 25 had measurement of serum cTnI at visit 3. Causes for missing serum cTnI include poor dog compliance or tertiary referral for procedure. At visit 1, there was no significant difference in serum cTnI concentration between the untreated (.05 ng/mL [0.02-0.13]) and atenolol groups (0.04 ng/mL [0.02-0.13], $P = .79$). The same was true at visit 2 (untreated 0.04 ng/mL [0.02-0.22] vs atenolol 0.04 ng/mL [0.02-0.17], $P = .83$) and visit 3 (untreated 0.04 ng/mL [0.02-0.14] vs atenolol 0.04 ng/mL

TABLE 3 Characterization of Holter variables recorded intraoperatively (between first cardiac intervention and removal of wires and catheters postballoon)

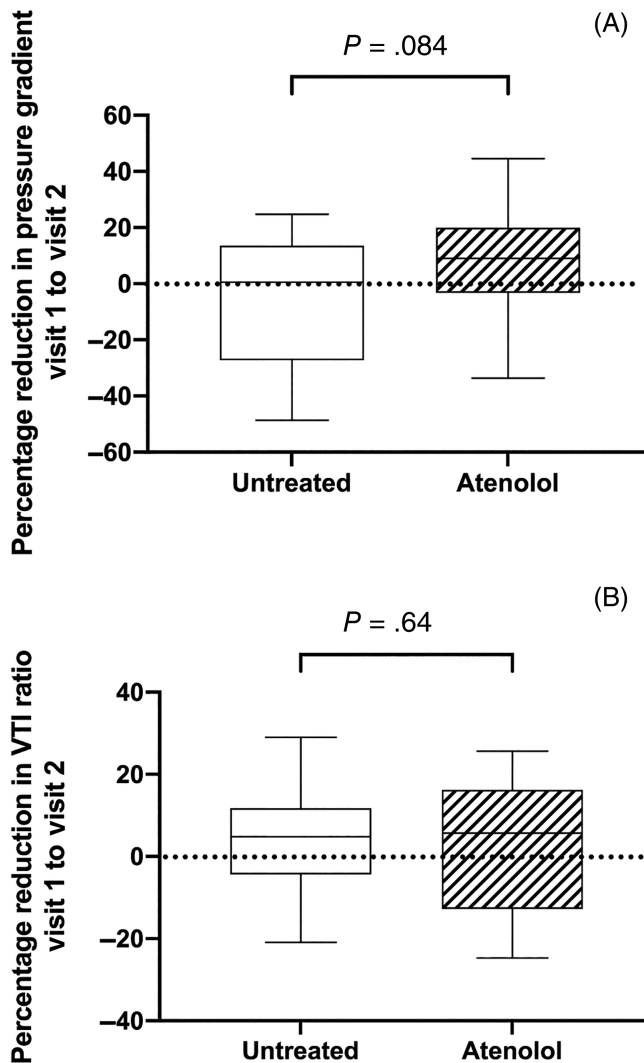
	Atenolol	Untreated	P value
VPC couplets	46 (0-481)	29 (3-121)	.59
VPC triplets	20 (0-265)	16 (1-82)	.67
Salvos of VPCs	9 (0-236)	4 (1-40)	.45
Salvo maximum rate (bpm)	213 (163-262)	219 (168-313)	.71
VT episodes	8 (0-224)	8 (1-118)	.99
VT maximum rate (bpm)	213 (153-283)	245 (138-302)	.2
VT longest run	19 (6-56)	14 (5-471)	.84
SVPCs	19 (0-881)	38 (2-285)	.43
SVT episodes	0 (0-20)	0 (0-6)	.86

Note: No significant differences between groups were identified. Results are expressed as median (range).

Abbreviations: SVPC, supraventricular premature complex; SVT, supraventricular tachycardia; VPC, ventricular premature complexes; VT, ventricular tachycardia.

**FIGURE 3** Number of dogs requiring vasopressors, glycopyrrolate or dobutamine intraoperatively, in order to treat hypotension. There was no significant difference in frequency between groups**FIGURE 4** Serum troponin I concentrations at each visit for both groups. No significant difference in troponin was detected after treatment with atenolol (visit 2 vs visit 1), nor was troponin concentration at visit 3 (after balloon dilatation) lower in the atenolol group

[0.02-0.07], $P = .9$). No significant difference in serum cTnI was detected after treatment with atenolol (comparing visit 2 to visit 1), nor did after balloon troponin reduce (comparing visit 3 and visit 1) in the atenolol group (Figure 4).

**FIGURE 5** Percentage reduction in (A) pressure gradient and (B) pulmonic to aortic velocity time integral (VTI) ratio between visits 1 (pretreatment) and 2 (after minimum 10-days from visit 1)

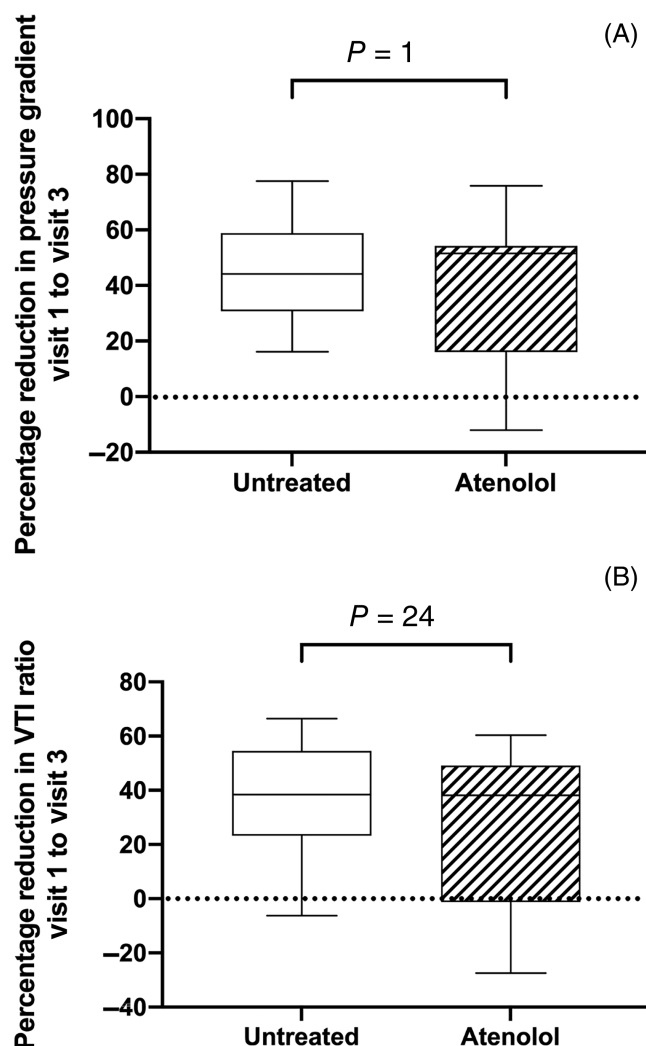


FIGURE 6 Percentage reduction in (A) pressure gradient and (B) pulmonic to aortic velocity time integral (VTI) ratio between visits 1 (pretreatment) and 3 (4-weeks postprocedure)

3.7 | Echocardiographic measurements

Before treatment, there was no significant difference in maximum pressure gradient between dogs allocated to the atenolol group or the untreated group: untreated 124 mm Hg (80-172 mm Hg) vs atenolol 119 mm Hg (64-160 mm Hg; $P = .86$). Similarly, after atenolol treatment, there remained no detectable difference between the groups: untreated 129 mm Hg (94-177 mm Hg) vs atenolol 106 mm Hg (61-151 mm Hg; $P = .57$). There was no significant difference between groups in either percentage reduction in pressure gradient or VTI ratio (Figure 5). At visit 3, after the procedure, the pressure gradient was reduced in all dogs compared with visit 1, but there was no significant difference in absolute pressure gradient between the groups: untreated 69 mm Hg (46-117 mm Hg) vs 61 mm Hg (24-105 mm Hg, $P = .71$). Once again, there was no significant difference detected between groups in the percentage reduction of pressure gradient or VTI ratio (Figure 6).

4 | DISCUSSION

Our results do not identify any benefits of preoperative treatment with atenolol before right-heart catheterization for balloon procedures in dogs with PS. We did not detect a reduction in the frequency of arrhythmias or the requirement for anesthetist intervention with antiarrhythmics or to tackle hypotension. Atenolol-treated dogs did not have a lower procedure time, nor a better outcome from the procedure. Serum cardiac troponin I measurements, used as a surrogate marker of ischemia, were not different between groups.

The effect of perioperative beta-blockers on arrhythmias in humans undergoing cardiac surgery is not well defined. It has been reported that preoperative use of beta-blockers for a minimum of 7 days substantially reduces the high burden of supraventricular and ventricular arrhythmias during cardiac surgery.¹⁵ However, a recent meta-analysis, which included several studies on perioperative beta-blocker use in adults undergoing cardiac surgery yielded a less clear-cut result. They found that beta-blockers “might” reduce ventricular arrhythmias (12 studies, 2296 participants), and atrial fibrillation (40 studies, 5650 participants), and the level of evidence provided by these studies was considered low.²⁵

The sample size calculation used for our study was based on a reduction of 20% in ventricular arrhythmia between groups, because we decided that this difference would be clinically meaningful, and was in fact lower than that described in the human literature.¹⁵

In this group of dogs, animals treated with atenolol had a lower heart rate, which is in accordance with previous studies,²⁶ and suggests an appropriate dose of atenolol for a degree of beta-blockade. It is possible that higher atenolol doses would have had a greater antiarrhythmic effect, but there is no data on which to base this in dogs. In addition, we did not measure plasma atenolol levels to account for individual pharmacodynamic variability. Polymorphisms of the beta-1 receptor have been identified in dogs, and these could also affect individual response to a given drug dose.²⁷ We did not attempt to account for this genetic variability in our study, so it could represent a confounding factor.

It has been anecdotally suggested that the negative inotropic and chronotropic effect of beta-blockers will facilitate positioning of cardiac catheters and guidewires and improve stability of balloon position during inflation thereby reducing procedure times for dogs on atenolol and improving their outcome. Although our study did not evaluate a qualitative measure of procedure ease, our data suggest that dogs receiving atenolol did not have a shorter procedure, fewer balloon inflations, or a better reduction in stenosis severity. Longer-term outcome was not assessed in this group of dogs.

The results of our study showed that atenolol was well tolerated in dogs. Side effects of atenolol reported in humans include cold extremities, fatigue, bronchospasm, and psychological depression.¹⁶ No specific questions were asked about cold extremities, but dogs receiving atenolol were no more lethargic, depressed, or exercise intolerant than the untreated group.

Beta-blockers can cause bradycardia, heart blocks, and hypotension.¹⁶ Our study did not show that dogs in the atenolol group

required more intervention to respond to hypotension than the untreated dogs. This is in accordance with a meta-analysis that suggested receiving a beta-blocker makes little or no difference to whether human patients experienced bradycardia or hypotension during cardiac surgery.²⁵

Beta-blockers reduce myocardial oxygen demand by their negative inotropic and chronotropic effects.¹⁶ Cardiac troponin-I is a marker of myocardial injury²⁸ and is increased in the presence of myocardial ischemia.²⁹ As such, we used this as a surrogate marker of myocardial ischemia. We did not identify a significant difference between treatment groups at any time point, which is in accordance with a previous study of cats with severe left ventricular hypertrophy, in which atenolol treatment did not reduce cTnI.³⁰ However, any effect of atenolol on serum cTnI concentrations might have been difficult to detect, as troponin concentrations were mostly within the reference interval for both groups, over all 3 visits and were therefore close to the lower limit of detection of the assay. This is in contrast with a previous study in which serum cTnI was increased in dogs with severe PS.³¹ This difference might reflect a different assay or sample handling technique, or simply differences which will invariably be present across different cohort of dogs, even with a single heart disease.

Our data showed that the change in transvalvular pressure gradient and VTI ratio was not different between groups. The absence of change in VTI ratio is in accordance with data from a different cohort of dogs with PS.²⁶ Our data supports the assertion by these authors that atenolol treatment in dogs with PS does not provide a benefit by increasing cross-sectional area for flow, but instead decreases right ventricular contractile function.

Our study is subject to several limitations. Although the anesthetic protocol was standardized for most dogs, different anesthetists were involved in this study. Each individual has a different threshold for intervening to treat hypotension, providing fluid boluses, or administering antiarrhythmic drugs. This could have affected our data, but we aimed to use this only as a secondary outcome measure. Moreover, a small number of dogs did not receive the preferred anesthetic protocol, and 1 dog received another antiarrhythmic at the beginning of the procedure. These decisions were made at the discretion of the anesthetist in the best interest of the dog, but might have affected our results in a relatively small study.

The procedures performed in this group of dogs sometimes included correction of other congenital defects as well as addressing the PS. In addition, our cohort of dogs included animals undergoing pulmonic transvalvular stent angioplasty. However, in all procedures performed, the right ventricle was catheterized and a balloon inflated to occlude cardiac output, which are the main triggers for arrhythmias during these procedures. Several cardiology residents and Board-certified cardiologists performed echocardiographic imaging or led procedures, which might introduce differences in technique. However, all echocardiographic measurements were performed by a single, blinded operator, and lead cardiologist for interventions was allocated dependent on clinic rotation.

Another limitation of this study is that the morphology of pulmonary valve stenosis in dogs is broad and this cohort of dog is

heterogenous. The effect of the drug intervention might have been biased by the morphology of the PS, concurrent diseases, degree of right ventricular remodeling, presence of right to left shunting lesions. Randomization of dogs to treatment groups might also have benefited from being stratified by valve morphology.

In conclusion, preoperative treatment with atenolol did not reduce the frequency of arrhythmias during the procedures carried out in this study. Treatment with atenolol was not associated with a reduced anesthetist intervention nor shorter procedure time. Atenolol use was not associated with reduced ischemic damage evidenced by a reduction in serum cTnI concentration when compared with untreated dogs. The findings of this study suggest that this group of dogs scheduled to undergo balloon procedures did not benefit from preoperative treatment with atenolol.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was reviewed and approved by the University of Bristol ethical review board, VIN/18/016.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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