THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Clinical presentation, management and survival in dogs with persistent atrial standstill in the United Kingdom.

Citation for published version:
Sanz-Gonzalez, I, Aitken , J, Pedro , B, Martin, M, Martinez-Pereira, Y, Dukes-McEwan, J, Bode , EF & Culshaw, G 2023, 'Clinical presentation, management and survival in dogs with persistent atrial standstill in the United Kingdom.', *Journal of Veterinary Cardiology*, pp. 1-30. https://doi.org/10.1016/j.jvc.2023.11.016

Digital Object Identifier (DOI):
10.1016/j.jvc.2023.11.016

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Journal of Veterinary Cardiology

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

OPEN ACCESS

Download date: 03. Dec. 2023

Clinical presentation, management and survival in dogs with persistent atrial standstill in the United Kingdom.

I. Sanz-Gonzalez LdoVet, MVetMed [a], J. Aitken BVSc [b], B. Pedro DVM, MSc [c], M. Martin MVB, DVC [d], Y. Martinez Pereira LdaVet [a], J. Dukes-McEwan BVMS, MVM, PhD [e], E.F. Bode BVSc, PhD [e,f] and G.J. Culshaw BVMS, PhD [a].

[a] Hospital for Small Animals, University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, Edinburgh, United Kingdom. [b]Faculty of Veterinary and Agricultural Sciences, University of Melbourne, Building 400, Parkville, Victoria, 3052, Australia. [c]Centro de Cardiologia Veterinaria do Porto, Rua Artur Maia Mendes 93, 4250-068, Porto – Portugal. [d]Veterinary Cardiology Consultancy, Kenilworth, CV8 2AA, United Kingdom. [e]Small Animal Teaching Hospital, School of Veterinary Science, University of Liverpool, Leahurst Campus, Chester High Road, Neston, CH64 7TE, United Kingdom. [f]ChesterGates Veterinary Specialists, Telford Court, Gates Lane, Chester, Cheshire, CH1 6LT, United Kingdom.

Corresponding author: sanz_vet@hotmail.com (Inigo Sanz-Gonzalez)

Acknowledgements: the authors would like to thank Sara-Ann Dickson, Dr. Catheryn Partington and Dr. Elzbieta Mederska for their assistance with the collection of data for this manuscript and Dr. Darren Shaw for his contribution to the statistical analysis.

Abstract:

Objectives: To investigate the clinical and echocardiographic presentation of dogs with persistent atrial standstill (PAS), identify variables measured at first presentation that could predict their survival and document the progression of the disease after pacing.

Materials and Methods: Retrospective study of medical records of dogs diagnosed with PAS at three referral hospitals of the United Kingdom over seven years.

Results: Twenty-six dogs were diagnosed with PAS during the study period. Median age of the population was three years (range: 7 months-12.5 years). The most common clinical sign was syncope (14/26). Twenty-four dogs received artificial pacemakers (PM). Major complications after PM implantation were observed in four dogs (4/24). Serial echocardiographic examinations showed that cardiac dimensions of PAS dogs with left atrial or left ventricular dilation at first presentation did not return to reference range after pacing. Further dilation of the cardiac chambers, recurrence of congestive heart failure (CHF) or development of new episodes of CHF were documented in 7, 4 and 10 PAS dogs despite pacing respectively. Median survival time for cardiac-related deaths after PM implantation was 1512 days (18-3207). Neither CHF nor echocardiographic variables at presentation predicted survival after PM implantation in PAS dogs.

Conclusions: PAS is an uncommon bradyarrhythmia, occurring in young adult dogs. Affected dogs were often presented with syncope. Whilst syncope resolved, cardiac remodelling persisted after PM implantation. Long-term survival was favourable after PM implantation and was not predicted by congestive status or cardiac chamber size at first presentation.

Key words: bradyarrhythmia, syncope, atrial cardiomyopathy, atrial paralysis, prognosis

Abbreviations:

CHF	Congestive heart failure
FS	Fractional shortening
LAmax	Left atrial diameter in short axis
LA:Ao	Left atrium to aorta ratio
LV	Left ventricle
LVIDd	Diastolic left ventricular internal diameter
LVIDdN	Diastolic left ventricular internal diameter normalized to body weight by allometric scaling.
MST	Median survival time
PAS	Persistent atrial standstill
PM	Pacemaker
SD	Standard deviation
UK	United Kingdom

Introduction

Atrial standstill is a rare condition characterized by a failure of atrial depolarization, leading to electrical and mechanical atrial inactivity [1].

In people, dogs and cats, temporary paralysis of the atria can result from electrolyte disturbances (hyperkalemia), anti-arrhythmic agents (digitalis glycosides toxicity, quinidine toxicity), myocardial infarction, myocarditis or hypoxia [2-5]. In these cases, the prognosis is favourable since correction of the triggering cause usually restores atrial activity.

By contrast, in persistent atrial standstill (PAS), progressive and permanent degenerative changes destroy the atrial myocardium, sinus node and internodal tracts resulting in irreversible changes (atrial cardiomyopathy) that lead to permanently “silent atria” with “paper-thin” walls [6-8].

The treatment of choice to alleviate the bradycardia-related clinical signs of canine PAS is pacemaker (PM) implantation [9]. Only up to 5% of dogs receiving a PM have PAS, and early reports on long-term prognosis of PAS suggested a relatively short survival time of only 12 to 18 months with a high incidence of death or euthanasia due to congestive heart failure (CHF) despite pacing [10-16]. More recently, isolated case reports and a multicenter retrospective study have been more favourable, recording survival times longer than two years after PM implantation [8,17,18]. Because of these conflicting datasets on survival, we reviewed the survival data of PAS dogs presented to three cardiology referral centers in the United Kingdom (UK) and, in particular, have investigated whether the conflicting survival data might represent distinct populations of dogs with different degrees of cardiac dilation at presentation. We hypothesized

that CHF and cardiac chamber enlargement at initial presentation predict survival after PM implantation in dogs with PAS.

To investigate this hypothesis, the objectives of our retrospective study were 1) to describe the clinical and echocardiographic presentations of dogs diagnosed with PAS; 2) to report their management and survival; 3) to identify variables measured at first presentation that could predict survival and 4) to document disease progression after pacing using measurements from follow-up echocardiographic examinations.

Animals, Materials and Methods

Data collection

This was a collaborative, multicenter, descriptive, retrospective study. A medical record search was performed to identify all dogs diagnosed with PAS between March 2006 and December 2013 at University of Edinburgh, University of Liverpool, and Willows Veterinary Centre.

Clinical records of affected dogs were reviewed to obtain the following information: signalment, weight, clinical signs, average heart rate at first presentation, the presence of a murmur, date of diagnosis, initial blood work, whether CHF was present at initial presentation based on thoracic radiographs or thoracic/abdominal ultrasound, the presence of concurrent non-cardiac diseases, medication before pacing, date of PM implantation and related minor or major complications, post-pacing development of CHF, outcome and survival.

Pre-pacing echocardiographic data obtained by multiple observers (board-certified cardiologist or resident in training under supervision) were reviewed and the following variables were extracted: left atrial diameter in short axis (LAmax) and left atrium to aorta ratio (LA:Ao) – both measured in early diastole, on the first frame of aortic valve

closure; diastolic left ventricular internal diameter (LVIDd), normalized diastolic left ventricular internal diameter (LVIDdN) and fractional shortening (FS). If LVIDdN was not available, it was calculated as follows: LVIDd in cm/body weight in $kg^{0.294}$ [19]. Additional echocardiographic findings, final diagnosis and comments made by the echocardiographers were also reviewed.

Dogs with increased serum potassium concentrations, receiving digitalis glycosides or with concurrent non-cardiac diseases were excluded from the study. Dogs that were not paced after diagnosis were excluded from follow-up and survival analysis.

Follow-up data collection

Echocardiographic measurements collected at <6 months post PM implantation were reviewed to assess the response to pacing therapy. In dogs that survived >12 months, echocardiographic data collected between 12-24 months post PM implantation were also analyzed.

All dogs undergoing PM implantation were included in follow-up and survival analysis. If the date and cause of death were missing from medical records, the owners or the referring veterinarian were contacted by phone or e-mail. The follow-up date limit was 31st May 2020, and the cause of death was considered cardiac if dogs died or were euthanized due to refractory CHF, recurrence of syncope, complications associated with pacing, or suffered a sudden unexplained death.

Statistical analysis

Data were analyzed with commercial software (Minitab 17 and GraphPad Prism 8). Normality was tested with the Anderson-Darling test. Continuous data are described as mean and standard deviation (SD) whereas non-normally distributed data are described as median and range. Categorical data were compared using the Chi-

squared test. The mean difference and SD of echocardiographic variables (LAmax and LVIDd) obtained at three different time points (presentation, within 6 months and within 24 months) were used to describe the magnitude of change in cardiac dimensions between visits. Survival analysis after PM implantation was assessed with Kaplan-Meier curves. Survival curves were compared with log-rank tests according to whether either CHF or diastolic left ventricular enlargement (using allometric scaling) was present at first presentation. Dogs still alive after 31st May 2020 and dogs lost to follow-up, were right censored. Significant differences were defined by $p < 0.05$.

Results

Demographic and clinical presentation:

Twenty-six dogs met the inclusion criteria. Of these, there were twelve entire females, six neutered females, four entire males and four castrated males. The female over-representation was not of statistical significance ($p=0.126$). Labrador retrievers, including their crosses, were the most common breed (9/26). The mean body weight of the population was 20.0 kg (SD 9.3) and median age was three years (7 months-12.6 years).

Mean heart rate at first presentation was 52 bpm (SD 12.8). The most common reason for presentation was pre-syncope or syncope (14/26) followed by lethargy and exercise intolerance (6/26), ascites (5/26) and cough (3/26). Two dogs (2/26) had no clinical signs apart from their incidental bradycardia.

Most dogs (20/26) had soft systolic murmurs: 12/20 grade II/VI, 4/20 grade III/VI, 3/20 grade IV/VI and 1/20 grade I/VI. These murmurs were most commonly audible over the apex (19/20 apical and 1/20 basilar) of the left hemithorax (left 12/20, right 1/20 and both 7/20).

At the time of initial presentation, 8/26 dogs (31%) were in CHF: 4/8 right CHF, 3/8 left CHF and 1/8 with biventricular CHF. Nine dogs (9/26) were receiving medication including theophylline (1/26) and CHF treatment (8/26): furosemide 6/8, pimobendan 5/8, benazepril 4/8 and spironolactone 3/8.

Signalment and clinical presentation data of the 26 dogs included in the study are summarized in Supplemental Table A (available on-line).

Echocardiographic findings at initial presentation in all PAS dogs:

Echocardiographic data at initial presentation were available for 25/26 dogs**.**

The left atrium was dilated in most dogs (23/25) and only 2/25 dogs had a LA:Ao ≤ 1.6. Median LA:Ao was 2.18 (1.53-3.65).

The left ventricular diastolic dimensions were above allometric reference ranges in 12/25 dogs and within normal limits in the other 13/25, with mean LVIDdN 1.87 (SD 0.37) [19]. Mean FS was 44% (SD 10.21) and all dogs with left ventricular dilation in diastole had FS > 25%.

Concurrent right atrial and right ventricular dilation was described in six dogs. One dog had an aberrant bronchoesophageal artery (dog #15) and four dogs had valvular changes (1/4 myxomatous mitral valve disease, 2/4 mitral valve dysplasia and 1/4 both mitral and tricuspid dysplasia). There was no apical displacement of the hinge points of the tricuspid valve in the single case of tricuspid valve dysplasia.

Echocardiographic data at initial presentation for paced PAS dogs are summarized in supplemental table B (available on-line).

Outcome and follow-up.

Non-paced dogs:

Two dogs (2/26, #5 and #15) were managed medically due to financial constraints. One was euthanized 19 days after its diagnosis due to refractory CHF and the other died suddenly during sleep 211 days after first presentation.

Paced dogs.

Pacing complications in the peri-operative period and short-term outcome (<6 months):

There were 24/26 dogs that underwent PM implantation. All dogs had single-chamber pacing devices inserted transvenously into the right ventricle. A right jugular approach (14/24) and active fixation leads (13/24 dogs) were most common. All dogs survived the procedure and were discharged.

One dog (#11) had a major complication during the peri-operative period consisting of cardiorespiratory arrest followed by successful resuscitation. Two other dogs (#4 and #13) had a minor peri-operative complication in the form of ventricular arrhythmias within 48 hours after PM implantation **(Figure 1).**

Major complications occurred in two dogs within 6 months of the procedure. There was macro-dislodgment of the pacing lead after 18 days in one dog (#21) that required a second procedure. Another dog (#1) experienced micro-dislodgement of the pacing lead first identified on day 40, resulting in recurrence of syncope. Loss of capture was observed when the patient was positioned in lateral recumbency. Modification of the delivered voltage temporarily controlled clinical signs but a second procedure was performed on day 1375.

One dog (#20) developed suspected exit block (loss of capture at 3.5V combined with normal lead impedance) first identified on day 35. Intermittent syncope resolved after pacemaker re-programming.

Two dogs developed CHF within 6 months of PM implantation: the first dog was euthanized due to refractory congestive heart failure (ascites) and worsening azotemia 18 days after pacing (#13) and the second dog developed pulmonary edema for the first time 62 days after pacing (#9).

Echocardiographic findings at <6 months post-pacing:

Seventeen of the 23 paced dogs that were still alive one month after pacing underwent an echocardiographic examination within 6 months of their procedure**.** Their echocardiographic data are summarized in supplemental table B (available on-line). In every case, left atrial or left ventricular dilation persisted where it had been identified prior to PM implantation.

Only one dog had an LA:Ao ≤ 1.6 (dog #25). This was one of the two dogs with LA:Ao ≤ 1.6 prior to pacing. The other dog had developed left atrial dilation (dog #21). The left atrium remained dilated in the other 15/17 dogs. The median LA:Ao was 1.84 (1.59-3.43).

Of the ten dogs with normal dimensions of the left ventricle (LV) before pacing, 7/10 maintained LV size within the reference range. In the other 3/10, dilation of the LV had developed (dogs #6, #9, #21). Of the seven dogs with increased dimensions at presentation, none of them had LV diameters within reference ranges after pacing. The mean LVIDdN was 1.95 (SD 0.38).

The mean difference in echocardiographic measurements obtained at presentation and within 6 months after PM implantation (n=17) was -0.12 cm (SD 0.68) for LAmax and 0.42 cm (SD 0.80) for LVIDd.

Complications and long term-outcome >6 months after PM implantation:

Twenty-one dogs (21/24) survived more than 12 months after PM implantation. Major complications occurred in one dog >6 months after its intervention. Macro-dislodgement of the pacing lead occurred 355 days after PM implantation. This dog (#6) did not undergo a second procedure due to financial constraints and was euthanized on day 374 due to refractory ascites **(Figure 1).**

Minor ventricular ectopy in the form of single ventricular premature complexes and couplets were detected in one dog 212 days after PM implantation (dog #7). No information about further investigations or anti-arrhythmic treatment was available.

Fourteen dogs (58%) developed CHF after pacing, most after the first six months (12/14, 86%). Of these, 10 dogs (71%) had not been in CHF prior to pacing but in 4 dogs (29%) it was a recurrence of pre-pacing CHF. Two (33%) of the 6 dogs that had been in CHF prior to pacing remained free from CHF by the end of the study period. Kaplan-Meier curve analysis revealed median time from pacing to development of CHF was 1699 days (range 18-3884).

Echocardiographic findings at 12-24 months post-pacing:

Echocardiography was performed in 12/21 dogs that survived longer than 12 months after PM implantation. These echocardiographic data are summarized in supplemental table B (available on-line).

All dogs had left atrial dilation (LA:Ao > 1.6), and median LA:Ao was 2.29 (1.62-3.16). Diastolic left ventricular dimensions were above the reference range in 7/12 dogs. Three of them had had normal diastolic left ventricular dimensions at < 6 months post pacing (dogs #7, #10, #11). Mean LVIDdN was 2.02 (SD 0.44) and mean FS was 35.5% (SD 6.83).

The mean difference in echocardiographic measurements obtained at presentation and within 12-24 months after PM implantation (n=11) was 0.65 cm (SD 1.06) for LAmax and 0.63 cm (SD 1.32) for LVIDd. The mean difference in echocardiographic measurements obtained within 6 months and 12-24 months after pacing (n=10) was 0.78 cm (SD 0.85) for LAmax and 0.46 cm (SD 0.73) for LVIDd.

Survival analysis

Twenty-four paced dogs were included in the survival analysis. By the end of the study period, 14/24 paced dogs had died, 9 /24 were alive and one case was lost to follow-up 1872 days after PM implantation **(Figure 1).**

Eleven dogs (11/14) had succumbed to refractory CHF. Only 1 dog died suddenly at home (1/14) – this dog had been receiving sotalol for ventricular tachycardia since the immediate post-operative period. Two dogs (2/14) were euthanized due to poor quality of life with non-specific clinical signs.

The median survival time (MST) for cardiac-related mortality after pacing was 4 years or 1512 days (18-3207). Survival rate at one year post-pacing was 84%; at two years it was 75%; at three years it was 66%; and at four years it was 55% **(Figure 2).**

Prognosticators of survival in paced dogs with PAS.

There was no difference in survival between dogs that were in CHF at first presentation (MST 1196 days) and those that were not (MST 1847 days), p= 0.628. Similarly, there was no difference in survival between dogs that had diastolic left ventricular enlargement at first presentation (MST 1512 days) and those that did not (MST 1847 days), p=0.608.

Discussion

This retrospective study summarizes the presentation, echocardiographic findings and survival of dogs diagnosed with PAS at three UK referral hospitals over a period of seven years. We demonstrate that PAS dogs treated with PM implantation have a median survival time greater than four years. We therefore conclude that pacemaker implantation is a feasible and successful management option for dogs with clinical PAS.

Cardiac chamber dilation was identified on echocardiography in nearly all the dogs prior to pacing. The majority of PAS dogs in our study had inappropriate bradycardia at first presentation. It is known that bradycardia induces rapid electrical, mechanical and structural adaption processes in cardiac myocytes that compensate for the reduction in cardiac output [20]. Volume overload due to bradycardia leads to eccentric hypertrophy of the ventricles and elongation of the ventricular myocytes [21]. However, over a period of up to 24 months, pacing did not lead to normalisation of the left-sided cardiac dimensions in any of the dogs of this study. Therefore, although we were unable to provide *post mortem* analysis, our echocardiographic data would suggest that bradycardia is not the sole contributor to the chamber dilation observed in PAS before pacing. Instead, persistence and progression of the cardiac dilation could reflect the underlying cardiomyopathy in solitude or in combination with the hemodynamic effects of single-chamber pacing. Histopathological changes that resemble arrhythmogenic right ventricular cardiomyopathy have been described in dogs with PAS [22]. These changes are considered irreversible, progressive and include atrophy and loss of myocytes with fatty or fibrofatty infiltration of the atrial myocardium, sinoatrial node, internodal tracts and atrioventricular junction [6-8, 22,23].

Our survival results are in broad agreement with median survival times of 866 days for all-cause mortality in paced PAS dogs obtained in a recent study [17]. They also

compare favourably with the five-year survival time described for dogs paced for any type of bradyarrhythmia in the UK [11]. Our study is at odds with the much poorer survival (12-18 months) described in early reports of PAS, which suggested that dogs diagnosed with PAS at a younger age may have shorter survival times either because of more malignant cardiac disease or because their PAS was part of a polysystemic disease involving skeletal muscles [12,14,18, 24-28]. Those studies describe stunted growth, marked atrophy of the temporal, shoulder and pelvic muscles, stiff gait, partial trismus and chronic regurgitation in affected dogs. None of these findings was reported in any of the dogs recruited in the current study. It is therefore possible that poorer outcome in previous reports reflects a different form of PAS with a different aetiology. For example, in people, multiple diseases and conditions are known to induce or contribute to atrial cardiomyopathies including hereditary muscular dystrophies, CHF, supraventricular arrhythmias, myocarditis, NPAA mutations, genetic repolarization disturbances, hypertension, obesity or diabetes [29].

Most dogs with non-PAS bradyarrhythmias are presented for PM implantation between 7-11 years of age, and most succumb to non-cardiac diseases rather than the development of CHF [10,12,13,30-33]. Our population of dogs was presented as young adults and most died from refractory CHF. These results were comparable with Cervenec *et al´*s population of PAS dogs with a median age of 3.5 years in which 64% suffered a cardiac-related death [17]. Serial echocardiography and follow-up examinations in our cases not only identified progressive dilation of cardiac chambers but also new episodes or recurrence of CHF despite PM implantation. Progression of the disease and CHF in paced PAS dogs is thought to occur because of ongoing destruction of the atrial myocardium leading to reduced ventricular filling and decreased production of atrial natriuretic peptide [15,22,25]. Our data demonstrate that

PAS will lead to cardiac-related death, and that survival in this younger population is comparable to that of older paced dogs with non-PAS bradyarrhythmias that die from non-cardiac age-related diseases [10,12,13,30-33].

Prognostication at first presentation with PAS seems challenging, and negative prognostic indicators used in other cardiac diseases, such as cardiac chamber size and congestive status, appear to have poor predictive value in PAS. We utilised echocardiographic measurements as a surrogate of cardiomyopathy severity and tested whether this could be used to predict outcome. The left atrium to aorta ratio was suspected to be a poor prognostic tool in canine PAS since left atrial dilation is a common feature in affected dogs. This was justified by our findings in which 52% of dogs had a LA:Ao at presentation between 1.8 and 2.5, clustering around the median. Diastolic left ventricular dimensions were used instead. Contrary to our hypothesis, we were unable to demonstrate a relationship between survival and diastolic left ventricular size or CHF prior to pacing. Our results are in agreement with previous studies [12,17] but should be interpreted with caution. The low number of dogs in our study, despite its multicenter nature, was similar to those in recent publications that included dogs with PAS [10-13,17,34] and not only demonstrates that PAS is uncommon but also reduced statistical power. This possibly prevented us from identifying CHF and heart sizes as contributors to survival (Type II errors) and meant that we were unable to determine the influence of multiple baseline variables through univariate and then multivariate Cox proportional hazards analyses.

In every case where pacing was successful, syncope resolved. While this does not address the incongruity between progressive chamber dilation despite an increased heart rate after pacing, we have at least demonstrated an association between low heart rate and syncope in PAS dogs. Our rate of major complications (17%) also

compares favourably with rates of 13-18% that have been recently published [30,32,34]. Based on these results, we believe that pacemaker implantation should be offered to the owner as an appropriate form of management when dogs with PAS are presented with syncope.

Labrador retrievers and their crosses were the most common breed in our study. This breed is the most frequently presented for PM implantation in the UK [10,11]. Our results may reflect the breed's popularity but familial inheritance of PAS of unknown mechanism is suspected in the Labrador and English Springer spaniel [17,23,26]. Human familial PAS has been associated with mutations of the natriuretic peptide precursor A, cardiac sodium channel SCN5A and Connexin-40 genes [29,35,36].

PAS in association with Ebstein´s anomaly has been reported in people [37,38]. Four dogs in our study had concurrent congenital cardiac abnormalities. To the authors' best knowledge, this is the first publication describing dogs with cardiovascular malformations and atrial standstill simultaneously.

There were several limitations relating to this study's retrospective nature. Pacemaker implantation technique and programming, echocardiographic protocols, CHF management and re-examination times were not standardized and results are limited by the accuracy of the patient records. Definitive diagnosis of PAS requires electrophysiological studies and cardiac mapping, which were not performed in any of these cases. Therefore, it is possible that some dogs had combinations of third-degree atrioventricular block with atrial fibrillation, sinus arrest or sinoatrial block [31]. The underlying cause of PAS in this population of dogs was unknown and *post mortem* examinations were not performed. Serum troponin I levels may have provided additional insight. However we excluded these results as they were only available for

14 dogs, were measured at different laboratories and were obtained at different timepoints relative to pacing. Finally, we excluded PAS dogs with concurrent systemic diseases, and our survival results only included cardiac-related deaths. Despite these limitations, we believe this study offers valuable, particularly prognostic, information to the clinician.

Conclusions:

In summary, the results of this study suggest that PAS is an uncommon bradyarrhythmia that occurs usually in young mature animals. Syncope resolved but cardiac remodelling persisted after pacemaker implantation. Long-term survival was favourable but was not predicted by congestive status or cardiac chamber size at first presentation.

References:

[1] Marini M, Arbustini E, Disertori M. Atrial standstill: a paralysis of cardiological relevance. Italian Heart Journal. Supplement 2004;5(9):681-6.

[2] Treseder JR, Scollan KF, Leblanc NL. ECG of the month. J Am Vet Med Assoc 2017;250(11):1242-1244.

[3] Bellmann B, Roser M, Muntean B, Tscholl V, Nagel P, Schmid M, Schauerte P. Atrial standstill in sinus node disease due to extensive atrial fibrosis: impact on dual chamber pacemaker implantation. Europace 2016;18(2):238-45.

[4] Spalla I, Spinelli D, Lucatini C, Memmi S, Magnoni R, Brambilla, P, Locatelli C. ECG of the month. J Am Vet Med Assoc 2014;244(1): 45-47.

[5] Tag TL, Day TK. Electrocardiographic assessment of hyperkalemia in dogs and cats. J Vet Emerg Crit Care 2008;18: 61-67.

[6] Correa-Salgado RA, Perez-Zapata JM. Four-year follow-up persistent atrial standstill in a dog. Israel Journal of Veterinary Medicine 2019;74(2): 102-107.

[7] Wesselowski S, Abbott J, Borgarelli M, Tursi M. Presumptive partial atrial standstill secondary to atrial cardiomyopathy in a Greyhound. J Vet Cardiol 2017;19(3):276-282.

[8] Schmitt KE, Lefbom BK. Long-term management of atrial myopathy in two dogs with single chamber permanent transvenous pacemakers. J Vet Cardiol 2016;18(2):187-93.

[9] Santilli RA, Giacomazzi F, Porteiro Vázquez DM, Perego M. Indications for permanent pacing in dogs and cats. J Vet Cardiol 2019;22:20-39.

[10] Fonfara S, Loureiro JF, Swift S, James RA, Pereira YM, Lopez-Alvarez J, Summerfield N, Dukes-McEwan J. English springer spaniels with significant bradyarrhythmias: presentation, troponin I and follow-up after pacemaker implantation. J Small Anim Pract 2010;51(3):155-61.

[11] Johnson MS, Martin MW, Henley W. Results of pacemaker implantation in 104 dogs. J Small Anim Pract 2007;48(1):4-11.

[12] Wess G, Thomas WP, Berger DM, Kittleson MD. Applications, complications, and outcomes of transvenous pacemaker implantation in 105 dogs (1997-2002). J Vet Intern Med 2006;20(4):877-84.

[13] Oyama MA, Sisson DD, Lehmkuhl LB. Practices and outcome of artificial cardiac pacing in 154 dogs. J Vet Intern Med 2001;15(3):229-39.

[14] Lai SR. Atrioventricular muscular dystrophy in a 5-month-old English springer spaniel. Can Vet J. 2009;50(12):1286-7.

[15] MacAulay K. Permanent transvenous pacemaker implantation in an Ibizan hound cross with persistent atrial standstill. Can Vet J 2002;43(10):789-91.

[16] Darke PGG, McAreavey D, Been M. Transvenous cardiac pacing in 19 dogs and one cat. J Small Anim Pract 1989;30: 491-499.

[17] Cervenec RM, Stauthammer CD, Fine DM, Kellihan HB, Scansen BA. Survival time with pacemaker implantation for dogs diagnosed with persistent atrial standstill. J Vet Cardiol 2017;19(3):240-246.

[18] Thomason JD, Kraus MS, Fallaw TL, Calvert CA. Survival of 4 dogs with persistent atrial standstill treated by pacemaker implantation. Can Vet J 2016;57(3):297-8.

[19] Cornell CC, Kittleson MD, Della Torre P, Häggström J, Lombard CW, Pedersen HD, Vollmar A, Wey A. Allometric scaling of M-mode cardiac measurements in normal adult dogs. J Vet Intern Med 2004;18(3):311-21.

[20] Verduyn SC, Ramakers C, Snoep G, Leunissen JD, Wellens HJ, Vos MA. Time course of structural adaptations in chronic AV block dogs: evidence for differential ventricular remodeling. Am J Physiol Heart Circ Physiol 2001;280(6):2882-90.

[21] Volders PG, Sipido KR, Vos MA, Kulcsár A, Verduyn SC, Wellens HJ. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. Circulation 1998; 98(11):1136-1147.

[22] Imai T, Ojiro R, Kimura Y, Machida N. Pathological Features of Persistent Atrial Standstill Syndrome in Three Dogs. J Comp Pathol 2020;180:9-15.

[23] Bomassi E, Rousselot J, Libermann S, Raymond Letron I, Etchepareborde S, Misbach C. Atrial cardiomyopathy in an adult Labrador retriever dog. Schweiz Arch Tierheilkd 2017;159(11):594-599.

[24] Nakamura RK, Russell NJ, Shelton GD. Adult-onset nemaline myopathy in a dog presenting with persistent atrial standstill and primary hypothyroidism. J Small Anim Pract 2012;53(6):357-60.

[25] Gavaghan BJ, Kittleson MD, McAloose D. Persistent atrial standstill in a cat. Aust Vet J 1999;77(9):574-9.

[26] Moïse NS. Inherited arrhythmias in the dog: potential experimental models of cardiac disease. Cardiovasc Res 1999;44(1):37-46.

436 [27] Tilley LP. Atrial Standstill. In: Lea and Febiger, editors. Essentials of canine and
437 feline electrocardiography: interpretation and treatment, 2nd ed. Philadelphia,1985,
438 p.164-9.

439 [28] Holland CT, Canfield PJ, Watson AD, Allan GS. Dyserythropoiesis, polymyopathy,
440 and cardiac disease in three related English springer spaniels. J Vet Intern
441 Med1991;5(3):151-9.

442 [29] Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS,
443 Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks
444 G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A,
445 Sanders P, Uribe W, Van Wagoner DR, Nattel S; EHRA/HRS/APHRS/SOLAECE
446 expert consensus on atrial cardiomyopathies: definition, characterization, and clinical
447 implication. Europace 2016;18(10):1455-1490.

448 [30] Ward JL, DeFrancesco TC, Tou SP, Atkins CE, Griffith EH, Keene BW. Outcome
449 and survival in canine sick sinus syndrome and sinus node dysfunction: 93 cases
450 (2002-2014). J Vet Cardiol 2016;18(3):199-212.

451 [31] Santilli RA, Porteiro Vázquez DM, Vezzosi T, Perego M. Long-term intrinsic rhythm
452 evaluation in dogs with atrioventricular block. J Vet Intern Med 2016;30(1):58-62.

453 [32] Lichtenberger J, Scollan KF, Bulmer BJ, Sisson DD. Long-term outcome of
454 physiologic VDD pacing versus non-physiologic VVI pacing in dogs with high-grade
455 atrioventricular block. J Vet Cardiol 2015;17(1):42-53.

456 [33] Hildebrandt N, Stertmann WA, Wehner M, Schneider I, Neu H, Schneider M. Dual
457 chamber pacemaker implantation in dogs with atrioventricular block. J Vet Intern Med
458 2009;23(1):31-8.

[34] LeBlanc NL, Agarwal D, Menzen E, Nomi K, Sisson DD, Scollan KF. Prevalence of major complications and procedural mortality in 336 dogs undergoing interventional cardiology procedures in a single academic center. J Vet Cardiol 2019;23:45-57.

[35] Disertori M, Quintarelli S, Grasso M, Pilotto A, Narula N, Favalli V, Canclini C, Diegoli M, Mazzola S, Marini M, Del Greco M, Bonmassari R, Masè M, Ravelli F, Specchia C, Arbustini E. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of Natriuretic Peptide Precursor A. Circ Cardiovasc Genet 2013;6(1):27-36.

[36] Groenewegen WA, Firouzi M, Bezzina CR, Vliex S, Van Langen IM, Sandkuijl L, Smits JP, Hulsbeek M, Rook MB, Jongsma HJ, Wilde AA. A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. Circ Res 2003;92(1):14-22.

[37] Carballal J, Asensio E, Hernández R, Narváez R, Gómez M, Dorantes J, Orea A, Rebollar V, Oseguera J. Ebstein’s anomaly, atrial paralysis and atrio-ventricular block: an uncommon association. Europace 2002;4(4):451-4.

[38] Piérard LA, Henrard L, Demoulin JC. Persistent atrial standstill in familial Ebstein's anomaly. Br Heart J 1985;53(6):594-7.

476 **Figure captions:**

477 **Figure 1. Flow chart summarizing the treatment and outcome of the 26 PAS dogs**
478 **included in the study.** CRP: cardiopulmonary resuscitation; PM: pacemaker.

479 **Figure 2. Kaplan-Meier survival analysis in 24 PAS dogs undergoing artificial**
480 **pacing (results showed in days).** Median survival time for cardiac mortality in PAS
481 dogs was 1512 days (18-3207).

482

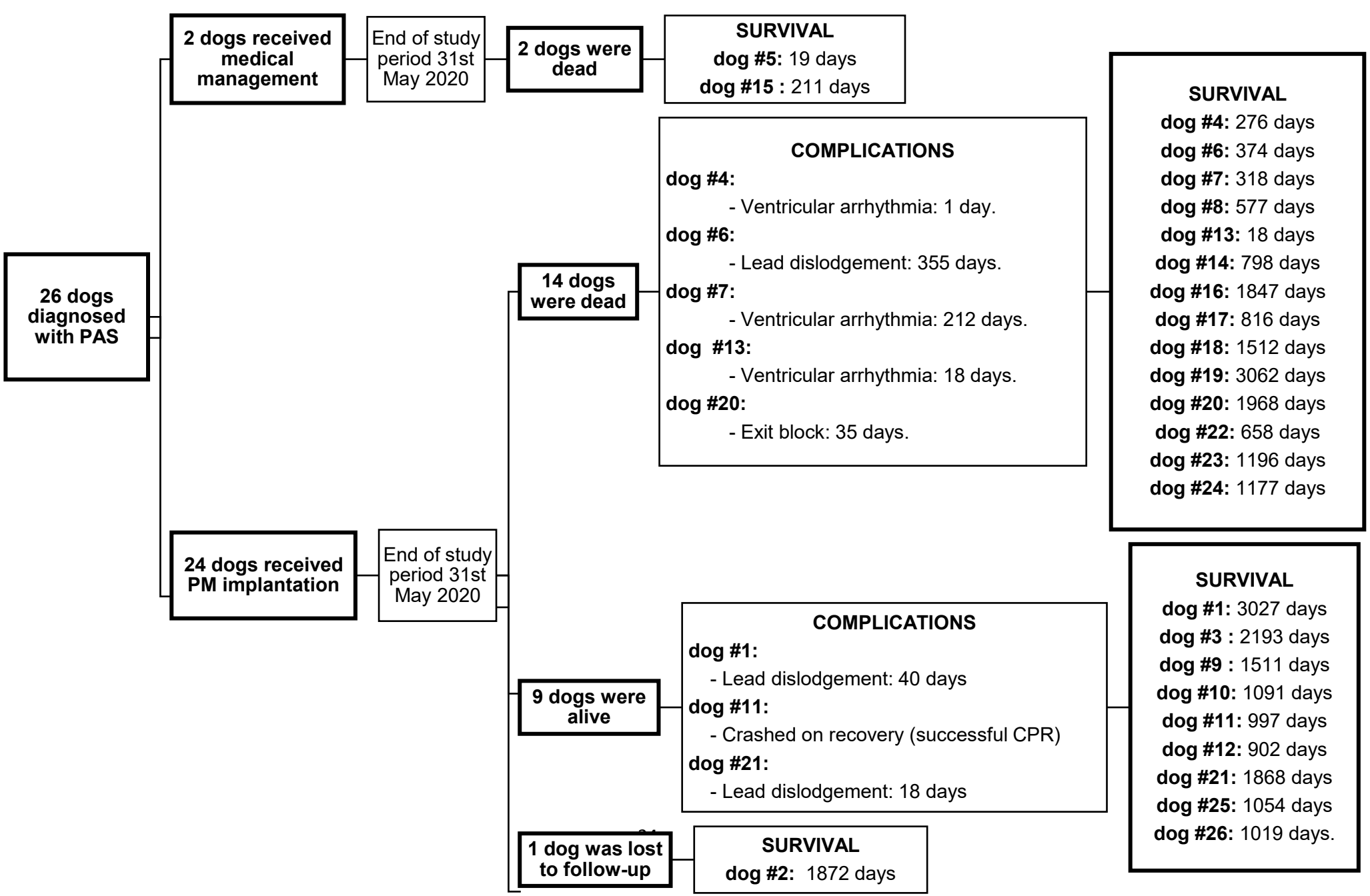
26 dogs diagnosed with PAS
2 dogs received medical management
End of study period 31st May 2020
2 dogs were dead
SURVIVAL
dog #5: 19 days
dog #15 : 211 days
24 dogs received PM implantation
End of study period 31st May 2020
14 dogs were dead
COMPLICATIONS
dog #4:
- Ventricular arrhythmia: 1 day.
dog #6:
- Lead dislodgement: 355 days.
dog #7:
- Ventricular arrhythmia: 212 days.
dog #13:
- Ventricular arrhythmia: 18 days.
dog #20:
- Exit block: 35 days.
SURVIVAL
dog #4: 276 days
dog #6: 374 days
dog #7: 318 days
dog #8: 577 days
dog #13: 18 days
dog #14: 798 days
dog #16: 1847 days
dog #17: 816 days
dog #18: 1512 days
dog #19: 3062 days
dog #20: 1968 days
dog #22: 658 days
dog #23: 1196 days
dog #24: 1177 days
9 dogs were alive
COMPLICATIONS
dog #1:
- Lead dislodgement: 40 days
dog #11:
- Crashed on recovery (successful CPR)
dog #21:
- Lead dislodgement: 18 days
SURVIVAL
dog #1: 3027 days
dog #3 : 2193 days
dog #9 : 1511 days
dog #10: 1091 days
dog #11: 997 days
dog #12: 902 days
dog #21: 1868 days
dog #25: 1054 days
dog #26: 1019 days.
1 dog was lost to follow-up
SURVIVAL
dog #2: 1872 days

Figure 1. Flow chart summarizing the treatment and outcome of 26 dogs with persistent atrial standstill included in the study. CRP: cardiopulmonary resuscitation; PM: pacemaker; PAS: persistent atrial standstill.

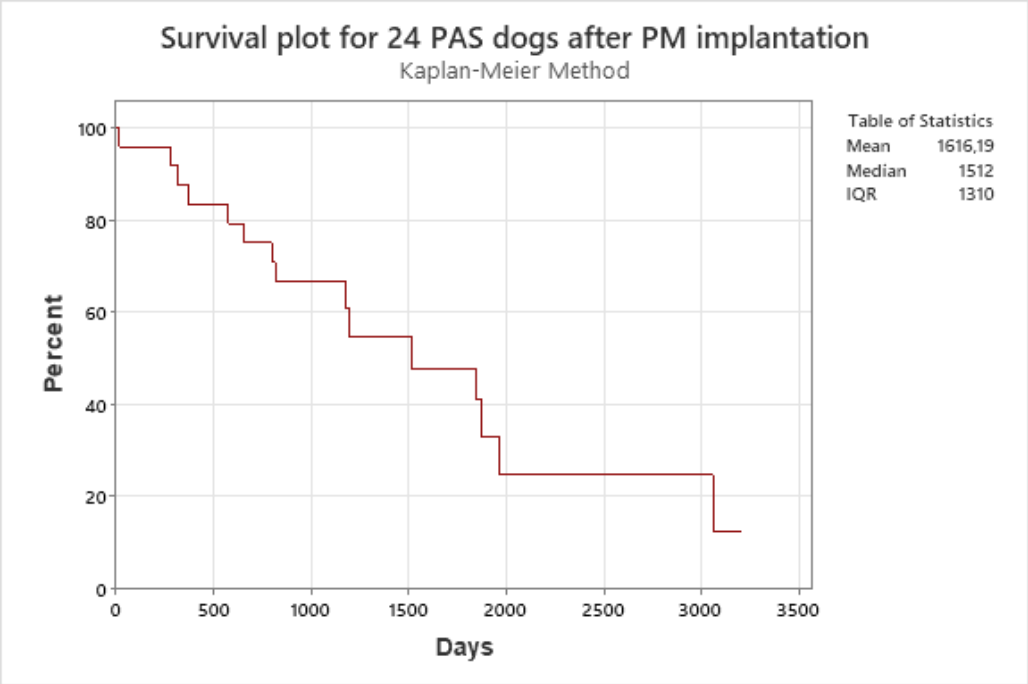

Figure 2. Kaplan-Meier survival analysis in 24 dogs with persistent atrial standstill undergoing artificial pacing (results showed in days). Median survival time for cardiac mortality in PAS dogs was 1512 days (18-3207). PAS: persistent atrial standstill.

Dog	Breed	Age (years)	Weight (Kg)	Gender	HR	Murmur	Clinical signs	CHF
#1	Nova Scotia Duck Tolling Retriever	0.6	15	FE	40	III/VI, L, A. III/VI, R,A.	None	No
#2	Toy Poodle	1.0	8	ME	50	IV/VI, L,A. III/VI, R,A.	Exercise intolerance	No
#3	Labrador	3.0	25	FN	50	II/VI, L,A.	Ataxia and lethargy	No
#4	Cross	2.0	21	FE	50	None	Syncope	No
#5	Shih Tzu	7.0	7	MN	60	III/VI, L, A. III/VI, R, A.	Syncope, dry cough, lethargy and anorexia	Yes
#6	English Springer Spaniel	2.0	18	M	32	II/VI, L A.	Several syncopal episodes	No
#7	Labrador Cross	4.0	26	MN	80	IV/VI,L, A	Wheezy breathing and occasional cough.	No
#8	Labrador	3.0	29	FN	56	II/VI, L, A. II/VI,R, A	Ascites and exercise intolerance	Yes
#9	Labrador Cross	4.0	25	ME	53	II/VI, L,A.	Syncope, weakness and reduced appetite	No
#10	Lhaso Apso	3.0	5	FE	64	II/VI, L, A. II/VI,R,A	Syncope, weakness	No
#11	Cavalier King Charles Spaniel	1.0	7	FE	40	II/VI, R, A	Cough, exercise intolerance and ascites	Yes
#12	Basset Fauve de Bretagne	7.0	18	ME	60	II/VI, L,A.	Exercise intolerance and lethargy	No

#13	Cavalier King Charles Spaniel	1.0	10	FE	36	None	Syncope, lethargy and ascites	Yes
#14	German Shepherd	2.0	21	FN	48	III/VI, L,A.	None	No
#15	English Springer Spaniel	4.0	24	MN	60	II/VI,L,A. II/VI,R,A.	Pre-syncopal episodes and cough	Yes
#16	Labrador	1.0	26	FN	60	II/VI,L,A. II/VI,R,A.	Lethargy	No
#17	Golden Retriever	7.0	29	FN	60	None	Syncope	No
#18	Lurcher	3.0	13	FE	52	None	Exercise intolerance and weakness	No
#19	Miniature Schnauzer	3.0	8	FE	/	None	Syncope and ascites	Yes
#20	Labrador	1.0	39	MN	40	I/VI, L, B.	Syncope and several weakness episodes	No
#21	Labrador	12.0	28	FN	72	II/VI, L, A.	Syncopal episodes	No
#22	Labrador Cross	3.0	23	FN	55	II/VI, L,A.	Syncopal episodes	No
#23	Brittany Spaniel	1.0	14	FE	35	None	Syncopal episodes	Yes
#24	Collie	10.0	16	FE	25	IV/VI, L,A.	Syncopal episodes	No
#25	Cane Corso	4.0	37	FE	45	II/VI, L,A.	Exercise intolerance	No
#26	Labrador Cross	5.0	28	FN	64	III/VI,L,A.	Cough	Yes
Summary		**Median:3 (0.6-12)**	**Mean:19.95 (SD: 9.27)**		**Mean:51.48 (SD: 12.90)**			

523

Supplemental table A. Signalment and clinical presentation of 26 dogs diagnosed with persistent atrial standstill in three referral centers of the UK. Two dogs (marked in grey) did not receive a pacemaker. *A: apical; B: basilar; CHF: congestive heart failure; FE: entire female; FN: neutered female; HR: heart rate; L: left; ME: entire male; MN: neutered male; R: right; SD: standard deviation.*

529

Dog	LA:Ao presentation	LA:Ao <6mo	LA:Ao 12-24 mo	LVIDdN presentation ($cm/Kg^{0.297}$)	LVIDdN <6mo ($cm/Kg^{0.297}$)	LVIDdN 12-24 mo ($cm/Kg^{0.297}$)	FS presentation (%)	FS <6mo (%)	FS 12-24mo (%)
#1	2.32	1.83	2.41	1.84	1.46	1.55	48	18	19
#2	3.28	1.76	1.82	2.05	2.07	1.81	46	37	30
#3	1.96	2.19	2.50	1.98	1.98	1.93	43	28	29
#4	2.18	3.43	/	1.85	2.25	/	35	45	/
#6	1.80	1.72	/	1.84	2.24	/	26	30	/
#7	2.91	2.85	/	2.76	2.78	/	42	/	/
#8	1.94	1.76	1.96	1.75	1.45	1.65	49	46	36
#9	1.82	1.82	/	1.71	1.96	/	49	35	/
#10	2.74	/	/	1.73	/	/	63	/	/
#11	1.96	1.76	2.17	1.72	1.74	1.77	47	36	39
#12	1.68	/	2.87	1.87	/	2.05	48	/	41
#13	1.65	/	/	1.37	/	/	39	/	/
#14	2.28	/	/	2.06	/	/	44	/	/
#16	2.42	/	/	1.63	/	/	30	/	/
#17	2.20	1.69	2.96	0.92	1.82	2.37	37	32	38
#18	2.66	2.95	3.16	2.38	2.71	3.17	44	50	41
#19	2.06	1.70	/	1.68	1.58	/	68	59	/
#20	1.86	1.82	/	1.58	1.81	/	34	34	/
#21	1.53	1.92	1.90	1.61	1.95	1.91	52	/	33
#22	2.82	1.89	3.15	1.85	1.68	2.33	35	20	43
#23	/	/	1.91	/	/	1.94	/	/	40
#24	2.92	/	/	2.43	/	/	50	/	/
#25	1.60	1.59	1.62	1.73	1.63	1.70	57	38	36
#26	1.93	1.97	/	1.99	2.09	/	25	20	/
Summary	**Median: 2.06 (1.53-3.28)**	**Median: 1.82 (1.59-3.43)**	**Median: 2.29 (1.62-3.16)**	**Mean: 1.87 SD: 0.37**	**Mean: 1.95 SD: 0.38**	**Mean: 2.02 SD: 0.44**	**Mean 43.96 SD: 10.71**	**Mean: 35.21 SD: 11.52**	**Mean: 35.45 SD: 6.83**

Supplemental table B. Echocardiographic follow-up in 24 PAS dogs that received PM implantation during the study: LA:Ao , LVlDdN and FS at presentation, within six months after PM implantation (<6mo) and 12-24 months post-pacing (12-24 mo). Note that dogs #5 and #15 have been excluded (not paced). *cm: centimetres; FS: fractional shortening; Kg: kilograms; LA:Ao: left atrium-to-aorta ratio; LVIDdN: diastolic left ventricular diameter normalised to body weight; mo: months; SD: standard deviation.*