Pacemaker-lead-associated thrombosis in dogs; a multicenter retrospective study

Introduction/objectives

Pacemaker implantation is recommended for the treatment of bradyarrhythmias causing clinical signs in dogs unresponsive to medical treatment. The most common canine arrhythmias requiring pacemaker implantation include high-grade second- and third-degree atrioventricular block and sick sinus syndrome [1-5]. Most permanent pacing leads are placed transvenously into the right ventricular apex because of the relative ease of placement and high success rates [2-4, 6]. Negative prognostic indicators include age, presence of concurrent cardiac disease, presence of congestive heart failure (CHF), presence of complications, presence of severe azotemia, using a secondhand pacemaker unit and increased troponin I levels [1, 2, 4, 5, 7]. Potential contraindications for transvenous pacing include small patient size or comorbidities, including pyoderma over the jugular vein insertion site, and epicardial pacing may serve as a suitable alternative [8]. Specific considerations for the method of cardiac pacing and treatment with anti-thrombotic therapy is often made by the clinician for patients in which a comorbidity causing a hypercoagulable state is suspected or diagnosed [9]. Diseases strongly associated with a hypercoagulable state in dogs include immune-mediated hemolytic anemia, protein-losing nephropathy (PLN) and protein-losing enteropathy, with weaker associations with a variety of conditions including severe pancreatitis, glucocorticoid administration and hyperadrenocorticism [9, 10].

Humans with intravascular foreign bodies including transvenous pacing leads are at increased risk of thromboembolic disease [11], and it is also recognized that dogs with transvenous pacing leads are at increased risk of thrombosis [9]. Pacemaker-lead-associated thrombosis (PLAT) is a well described phenomenon in people, with PLAT

documented in up to 45% of people following permanent transvenous pacemaker implantation and occurring either on the lead within the heart or on the lead within the venous system [12-18]. Although the majority of people with PLAT are asymptomatic, serious thrombotic and embolic complications are reported in 0.6%-3.5% [19], including risk of sudden death [20].

Existing literature on the occurrence and clinical importance of PLAT in dogs is scant and is limited to individual case reports or small case series [21-23] or recorded as a complication in the outcomes of larger studies on transvenous pacing [1, 6, 7, 24]. Previous experimental studies have identified thrombi associated with pacing leads in 33.7% of dogs at necropsy [25], however there are no studies specifically investigating PLAT in clinical dogs. Treatment modalities following diagnosis of PLAT in humans include medical management with anti-thrombotic medications or thrombolysis, or interventional procedures including thrombectomy or lead extraction [19]. Treatments reported in case reports in dogs following PLAT diagnosis include medical management with unfractionated heparin, rivaroxaban, local infusion of recombinant tissue-plasminogen activator, and balloon venoplasty [21-23]. There is no treatment consensus in humans or dogs with PLAT. The prognosis for dogs following identification of a thrombus is unknown.

The aim of this study was to identify the proportion of dogs developing PLAT following permanent transvenous pacemaker implantation, describe the treatment received and clinical outcome in these dogs, and to identify potential risk factors for the development of thrombi.

Animals, materials and methods

Data collection

A retrospective medical search was performed in seven referral centers[a-g] for all dogs with a permanent pacemaker implanted between January 2012 and January 2019. Ethical approval was granted at the primary investigator's center (VIN/19/013). A proportion of dogs from one center have been previously described [5]. Dogs were divided into three groups: group one: dogs with a transvenous pacemaker with at least one follow-up echocardiogram performed, group two: dogs with a transvenous pacemaker without follow-up echocardiography performed, and group three: dogs with an epicardial pacemaker. Dogs in group one were subdivided into dogs positive or negative for PLAT. Dogs were deemed positive for PLAT if a mobile or immobile mass-like vegetative lesion was identified within the venous lumen or within the right heart associated with a pacemaker lead on follow-up imaging (Fig. 1), with a lack of clinical signs supportive of endocarditis at the time of identification.

For all groups, data collected included signalment, rhythm diagnosis, comorbidities and echocardiographic findings at the time of pacemaker implantation. The rhythm diagnosis was based on the medical records and dogs were grouped into one of: 'atrioventricular block', 'atrial standstill', 'sinus arrest', 'sinus node dysfunction/sick sinus syndrome' and 'vagally mediated'. Comorbidities were classified based on organ system involved rather than individual disease process. Echocardiography was performed by a board-certified specialist or resident in cardiology under the supervision of a board-certified Diplomate. Echocardiographic data included 2D short axis left atrial to aortic ratio [26], M-mode end-diastolic left ventricular

internal diameter normalized for body weight [27], M-mode left ventricular fractional shortening, a subjective assessment of right atrial size (compared to left atrial size, being reported as either ‘<50%’, ‘50-100%’ or ‘>100%’ of left atrial size), a subjective assessment of right ventricular size (compared to left ventricular size, being reported as either ‘<50%’, ‘50-100%’ or ‘>100%’ of left ventricular size) and information on any other echocardiographic abnormalities. Where available, results of serum albumin, urine protein:creatinine ratio (UPCR) and thromboelastography (TEG) analysis performed within 30 days of pacemaker implantation were collected. Hypoalbuminemia was defined as a serum albumin below the reference interval as defined by each center, or, in the absence of access to blood results, as a medical record reporting hypoalbuminemia. Proteinuria was defined as a UPCR >0.5, or, in the absence of access to urine results, as a medical record reporting proteinuria. A hypercoagulable TEG was based on the interpretation of the clinician in charge of the case. For dogs with transvenous leads, additional data on active versus passive lead and single versus dual chamber pacing was collected, as was data on anti-thrombotic medications prescribed during hospitalization and at discharge. For dogs with epicardial leads, the reason for choosing an epicardial pacemaker was collected. For all dogs, pacemaker related complications, including suspected thromboembolic events, survival time from pacemaker implantation and reason for death were recorded.

For dogs diagnosed with PLAT, comorbidities and, where available, serum albumin and UPCR at the time of PLAT diagnosis were collected. Details on the treatment of each dog following PLAT diagnosis, clinical signs related to the thrombus

and findings on follow-up echocardiography (presence or absence of PLAT), if performed, were recorded. Survival time from PLAT diagnosis was calculated.

Statistical analysis

Statistical analysis was performed using commercially available software[h]. Normality of the data was assessed using a combination of visual examination of histograms, Q-Q plots and Kolmogorov-Smirnov tests. Non-normally distributed data are reported as median (inter-quartile range). Comparisons of variables between two groups were performed using Mann-Whitney U tests for continuous non-normally distributed data. Comparisons of variables between more than two groups were performed using Kruskal-Wallis tests with Dunn's post hoc analysis for non-normally distributed data. Categorical variables were compared using the chi-squared test or Fischer's exact test as appropriate. Post hoc analysis of the chi-squared test was performed by assessing the adjusted residuals. Statistical significance was set at $P<0.05$ for all analyses, with a Bonferroni correction applied to reported P values for multiple comparisons. Kaplan-Meier survival curves were generated looking at all-cause mortality. Continuous variables were split into quartiles for the purposes of analysis. The Log-Rank test was used to assess for the impact of baseline characteristics at the time of pacemaker implantation, as well as the presence of PLAT, on survival. Survival times are reported as median (range). To evaluate the effects of multiple variables on survival, multivariable analysis was performed using variables significant at $P<0.10$ using a backward selection stepwise Cox regression model. Colinearity was checked using Pearson correlation.

Results

Whole population

Permanent pacemakers were placed in 606 dogs from seven referral centers in the UK and USA (Fig. 2, Table 1). Median age for the population was 9.7 years (7.1-11.7 years) and females were the predominant sex (n=345, 56.9%). The population consisted of 86 different breeds, with the most common breed being mixed breed dogs (n=62, 10.2%). The most common rhythm was atrioventricular block (n=430, 71.0%), and a minority of dogs (n=58, 9.6%) were in CHF at the point of pacemaker implantation. Comorbidities (Fig. 3) were present in a majority of dogs (n=458, 75.6%), the most common comorbidities being cardiac (n=354, 58.4%) and urinary (n=91, 15.0%). The most common cardiac comorbidity was myxomatous mitral valve disease (n=284, 46.9%). Of the 143 dogs in which a UPCR was measured, 65 had increased levels. An additional 12 dogs had proteinuria reported in their clinical notes without evidence of a UPCR being measured. Three dogs (0.5%) had evidence of thrombotic disease at the point of pacemaker implantation, one with a pulmonary thromboembolism (PTE) and two with a splenic thrombus. The dog with a PTE had a transvenous lead placed and did not develop PLAT. This dog received long-term treatment with clopidogrel and enalapril for a PLN and had no further thrombotic events reported. Both dogs with a splenic thrombus had epicardial leads placed. One dog had a splenectomy and was treated with long-term clopidogrel, and the other dog was treated with a continuous rate infusion of heparin whilst hospitalized, discharged on a 14-day tapering

course of subcutaneous heparin, and received long-term treatment with clopidogrel. No further thrombotic events were reported in these patients.

Of the 606 dogs, 260 dogs (43%) had a transvenous pacemaker placed with echocardiographic follow-up performed (group one), 268 dogs (44%) had a transvenous pacemaker placed without echocardiographic follow-up (group two) and 78 dogs (13%) had an epicardial pacemaker placed (group three). There were significant differences in the distribution of groups between the centers (Fig. 4), with center five not placing any epicardial pacemakers and center six placing more epicardial pacemakers than average. There were some differences in baseline characteristics between the groups (Table 1). Dogs with transvenous pacemakers without echocardiographic follow-up were older than either of the other two groups, and dogs with epicardial pacemakers weighed less than those with transvenous pacemakers that underwent echocardiographic follow-up. Dogs with atrial standstill were more likely to receive echocardiographic follow-up. There were statistically, but not clinically, significant differences in left atrial to aortic ratio, end-diastolic left ventricular internal diameter, serum albumin and length of hospitalization between groups. Dogs with epicardial leads were more likely to be proteinuric compared to either of the other groups.

The most commonly reported indications for choosing epicardial pacing were due to a protein-losing enteropathy or PLN (n=23, 29.5%) and patient size or demeanor (n=16, 20.5%) (Table 2).

Of the 528 dogs with transvenous pacemakers, the majority received single chamber pacemakers (n=477, 90.3%). More than half of leads implanted in the ventricle used active fixation (n=321, 60.8%) whereas it was slightly more common for the leads

implanted in the atrium to use passive fixation (n=29, 58.0%) (Table 3). Of the dogs with transvenous pacemakers, twenty-five (4.7%) were discharged on anti-thrombotic medications. Twenty-two of the twenty-five (88.0%) dogs received one anti-thrombotic medication (clopidogrel n=18 (72.0%), aspirin n=3 (12.0%), low-molecular-weight heparin n=1 (4.0%)) and three (12.0%) dogs received two anti-thrombotic medications (clopidogrel and aspirin n=2 (8.0%), clopidogrel and low-molecular-weight heparin n=1 (4.0%)). Dogs discharged on anti-thrombotic medications included both dogs identified as being hypercoagulable on TEG, one of which had a PTE on pre-pacemaker assessment.

Pacemaker-lead-associated thrombosis population

Pacemaker-lead-associated thrombosis was identified in 27/260 (10.4%) dogs with echocardiographic follow-up. Median time from pacemaker implantation to PLAT diagnosis was 175 days (6-1,853 days). Echocardiography identified the thrombus on the lead in 26/27 (96.3%) dogs, whereas computed tomography was required to identify the thrombus in one dog. Location of the thrombus was reported as the right atrium in 17/27 (63.0%), right ventricle in 6/27 (22.2%), cranial vena cava in 3/27 (11.1%), and cranial vena cava and left brachiocephalic vein in 1/27 (3.7%). In two of the dogs with a right atrial thrombus, the thrombus was also documented to extend into the cranial vena cava. In two of the dogs with a right ventricular thrombus, a thrombus was also documented in the right branch of the pulmonary artery. The PLAT was considered an incidental finding in 15/27 (55.6%) dogs. Of the 12 dogs with PLAT and clinical signs, six (50.0%) had a suspected PTE causing tachypnoea, two of which also had evidence

of right sided CHF (ascites 1/12 (8.3%), pleural effusion 1/12 (8.3%)), four (33.0%) had right sided CHF (pleural effusion 2/12 (16.7%), ascites 1/12 (8.3%), pleural effusion and trace ascites 1/12 (8.3%)), and two (16.7%) had biventricular CHF (pulmonary edema and ascites). Two of the dogs with right sided CHF had chylothorax suspected to be caused by the obstruction of the cranial vena cava by the PLAT. No dogs had any signs of peripheral edema or head swelling.

At pacemaker implantation, dogs that went on to be diagnosed with PLAT had a higher UPCR, were more likely to be diagnosed as proteinuric and had a higher left ventricular fractional shortening than those with echocardiographic follow-up that were not diagnosed with PLAT. There were no other significant differences between those with echocardiographic follow-up that did and did not get diagnosed with PLAT (Table 4). None of the dogs with PLAT had a TEG performed at pacemaker implantation.

Comorbidities were reported in 23/27 (85.2%) dogs at the time of PLAT diagnosis. The most common comorbidities included urinary disease (PLN (n=8, 29.7%), chronic kidney disease and PLN (n=1, 3.7%), renal cyst (n=1, 3.7%) and unspecified renal disease (n=1, 3.7%)), myxomatous mitral valve disease (n=8, 29.7%) and endocrine disease (hyperadrenocorticism (n=2, (7.4%), suspected hyperadrenocorticism (n=1, 3.7%) and thyroid tumor (n=1, 3.7%)). Serum albumin was measured in 15/27 (55.6%) dogs, with a median (inter-quartile range) of 28.5 g/L (25.0-31.0 g/L). Hypoalbuminemia was reported in 6/15 (40.0%) dogs. Urine protein:creatinine ratio was performed in 12/27 (44.4%) dogs, with a median (inter-quartile range) of 2.21 (0.60-5.53). Proteinuria was present in 10/12 (83.3%) dogs.

Six dogs were receiving anti-thrombotic medications at the time of PLAT diagnosis (Fig. 5), all receiving anti-platelet medications (clopidogrel and/or aspirin). Indications for anti-thrombotic medications were reported in four (66.7%) of these dogs and included PLN (clopidogrel n=1 (25.0%), aspirin n=1 (25.0%)), protein losing enteropathy (clopidogrel n=1 (25.0%)) and suspected hyperadrenocorticism (aspirin n=1 (25.0%)). Five of the six (83.3%) dogs already receiving anti-thrombotics at the time of PLAT had an additional anti-thrombotic added at the point of PLAT diagnosis (addition of an anti-platelet n=2 (40.0%), addition of an anti-coagulant n=3 (60.0%)). Sixteen out of 21 (76.2%) dogs naïve to anti-thrombotic medications at the time of PLAT diagnosis started anti-thrombotics (anti-platelet n=12 (75.0%), anti-platelet and anti-coagulant n=4 (25.0%)) following identification of PLAT. No patients received thrombolytic medications, or had any interventional procedures with thrombectomy or lead extraction.

Median survival time from PLAT diagnosis was 81 days (0-1,103 days). Two dogs died on the day of PLAT diagnosis. One of which had a sudden cardiopulmonary arrest and the other was euthanized due to suspected PTE. Follow-up echocardiography was performed in 15/25 (60.0%) dogs that survived to discharge following PLAT diagnosis and the thrombus resolved in 9/15 (60.0%) dogs. Seven of the nine (77.8%) dogs in which the thrombus resolved were receiving anti-thrombotic medication (clopidogrel n=5 (55.5%), clopidogrel and aspirin n=1 (11.1%), clopidogrel, aspirin and low molecular weight heparin n=1 (11.1%)), while two out of nine (22.2%) dogs had thrombus resolution without anti-thrombotic therapy. Thrombus resolution was not documented on follow-up echocardiography in 6/15 (40.0%) dogs, all of which were receiving anti-thrombotics (clopidogrel, aspirin and low molecular weight heparin n=2

(33.3%), clopidogrel and low molecular weight heparin n=2 (33.3%), aspirin n=1 (16.7%), clopidogrel n=1 (16.7%)). There was no association between number of anti-thrombotic medications prescribed and resolution of the thrombus (P=0.322). At final follow-up, 22/27 (81.7%) dogs with PLAT had died and 119/232 (51.3%) non-PLAT dogs had died. Dogs with PLAT had shorter survival times from implantation compared to those without PLAT (Fig. 6).

Whole population complications and outcome

In 102/606 (16.8%) dogs there was at least one complication reported that was considered to be directly related to the pacemaker. The complications reported were lead dislodgement (n=27, 4.5%), lead thrombus (n=27, 4.5%), wound related complications (n=22, 3.6%), surgical or general anesthetic related complication (n=8, 1.3%), development of systolic dysfunction (n=7, 1.2%), myocardial perforation (n=6, 1.0%), lead infection (n=4, 0.7%), exit block (n=3, 0.5%), lead fracture (n=1, 0.2%), generator movement (n=1, 0.2%) and noise reversion (n=1, 0.2%).

In the whole population, 18/606 (3.0%) had a clinically suspected thromboembolic event after pacemaker implantation. Six (33.3%) of these were suspected arterial thromboembolic events (four (22.2%) with neurological signs where a thromboembolic event was considered most likely, two (11.1%) to the hindlimbs) and 12 (66.7%) were PTEs. Of the 12 dogs with PTEs, 10 (83.3%) had transvenous leads and two (16.7%) had epicardial leads. Seven of the 10 (70.0%) dogs with a transvenous

lead and a PTE had PLAT identified, and three (30.0%) did not, one of which had a jugular vein thrombosis suspected but not confirmed.

Follow-up was available for 600/606 (99.0%) dogs. At final follow-up 347/600 (57.8%) were dead, with death being considered related to the heart or pacemaker in 84/347 (24.2%). Of these 84, 14 (16.7%) were sudden deaths and seven (8.3%) were suspected PTEs in dogs with transvenous leads (six of whom had PLAT identified). Other causes for death were neoplasia (n=56, 16.1%), neurological disease (n=23, 6.6%), renal disease (n=21, 6.1%), suspected PTEs in dogs with epicardial leads (n=2, 0.6%), hindlimb arterial thromboembolism (n=1, 0.3%), other (n=69, 19.9%) and unknown (n=91, 26.2%). Overall survival time for the population was 907 days (0-2,661 days). Factors associated with a longer survival time on univariable analysis included younger age and not being neutered. Factors associated with a shorter survival time on univariable analysis included being underweight (body condition score ≤3/9), presence of comorbidities, being in CHF, being in the top or bottom left atrial to aortic ratio quartile, right atrial enlargement, right ventricular enlargement, hypoalbuminemia, experiencing pacemaker complications and having PLAT (Table 5, Fig. 6). It was not possible to generate a multivariable Cox proportional hazards model as all models generated violated the assumptions of the model.

Discussion

Our study documented PLAT in 27/260 (10.4%) of dogs with echocardiographic follow-up. We have also identified an association between proteinuria at pacemaker

implantation and later development of PLAT. Finally, we have shown that those dogs with PLAT have a shorter survival time from pacemaker implantation than those that have not been documented to develop PLAT.

The incidence of PLAT in dogs following placement of a permanent transvenous pacemaker was previously unknown, with dogs diagnosed ante-mortem with PLAT described in case reports or case series [21, 22], or as complications of larger studies of dogs with pacemakers, with incidence varying from 0.6-6.1% [1, 6, 7, 24]. In a post-mortem study 33.7% of dogs had PLAT identified, with the thrombus most often identified 10-60 days post implantation [25]. The median time to identification of PLAT in our study was 175 days, however it ranged from 6-1,853 days, documenting PLAT as a potential complication in both the short-term and long-term period following pacemaker implantation.

From a post-mortem study, the most common location for PLAT in dogs was the right atrium [25]. Ante-mortem reports in dogs predominantly report intra-cardiac PLAT [7, 24] and, where specified, this is usually within the right atrium [6], sometimes obstructing right heart inflow [21]. However, there are individual reports of thrombosis of the lead as it passes through the cranial vena cava [1] and thrombosis of the lead in the jugular vein and cranial vena cava as well as thrombosis of the right cephalic vein [22] reported. This is in concordance with our report where 23/27 (85.2%) dogs had intra-cardiac PLAT and the right atrium was the most common location. Only 4/27 (14.8%) dogs had solely cranial vena cava PLAT, and two additional dogs had extension of the right atrial PLAT into the cranial vena cava. One dog in our study with a PTE was suspected to have jugular thrombosis but this was not confirmed and so not considered

to have PLAT. In the human literature PLAT has been more comprehensively reported. Right atrial PLAT was initially thought to be uncommon, with a 2004 review of the human literature identifying only 24 cases [16], however a more recent review suggests a higher incidence of up to 38% [17]. Venographic studies in humans have documented a higher incidence rate of venous thrombosis, with up to 45% people found to have a venous thrombus after transvenous pacemaker placement [12-15, 18]. The apparent difference in location of PLAT between dogs and people is likely due to the imaging modalities used, with most dogs only undergoing echocardiography, whereas the venous thrombi were identified following venographic studies which are not commonly performed in dogs.

In our study PLAT was considered an incidental finding with no clinical signs in 15/27 (55.6%) dogs with the remaining dogs experiencing PTE and/or CHF. There is a similar mix of clinical presentations in the veterinary literature. Some papers consider PLAT to be a minor complication with no reported clinical signs [1, 6, 25] whereas others report it as a major complication [7, 21, 22, 24] due to the development of PTE or cranial caval syndrome. Some of the variation in the literature may represent different centers approaches to follow-up in these patients – we have demonstrated that many dogs do not undergo echocardiographic follow-up post pacemaker implantation and so it is likely that silent PLAT will not be diagnosed in these dogs. A proportion of dogs may only have undergone echocardiography because they had clinical signs of PLAT, thereby selecting the most severely affected. Humans with intravascular foreign bodies including transvenous pacing leads are at increased risk of thromboembolic disease [11], with serious thrombotic and embolic complications reported in 0.6%-3.5% [19],

388 including risk of sudden death [20]. The majority of people with venous thrombosis are
389 asymptomatic, although up to 10% are reported to have clinical signs secondary to
390 thrombosis [12, 14, 15, 18]. Early reports suggested that more than 80% of people with
391 right atrial PLAT presented acutely or sub-acutely with signs of heart failure, shock,
392 shortness of breath, chest pain, malaise, cyanosis and oedema [16]. However, more
393 recent studies have shown an unclear relationship between intra-cardiac PLAT and PTE
394 [17]. There is concern in people about an intra-cardiac PLAT causing a paradoxical
395 embolus in those with a patent foramen ovale [17]. In our study, six dogs had suspected
396 arterial thromboembolic events and in one previous study a dog died due to an aortic
397 thromboembolism [24]. However, it is impossible to prove whether these were
398 paradoxical emboli related to PLAT or an incidental finding.

399 Studies on specific risk factors for PLAT are lacking and, where present in the
400 human literature, conflicting. One study [14] identified absence of anti-coagulant therapy
401 and multiple pacing leads as risk factors for development of thrombosis, whereas an
402 earlier study [12] did not find these associations. The presence of CHF has been
403 reported to be inversely related to the development of thrombosis in people, although
404 this was considered likely related to people with CHF receiving anti-coagulant therapy
405 rather than a direct protective effect of CHF. In our study, presence of CHF at the time
406 of pacemaker implantation or number of pacemaker leads were not associated with
407 PLAT. Results of our study show that dogs with PLAT were significantly more likely to
408 have proteinuria at the time of pacemaker implantation than dogs without PLAT.
409 Significant proteinuria was also common at the time of PLAT diagnosis. The cause of
410 proteinuria could not be determined in all dogs in our study population due to the

411 retrospective nature of the study and so full biochemical and urine analysis results were
412 not always available.

413 Risk factors for thrombosis are well described, with the CURATIVE guidelines
414 defining dogs with PLN as a ‘high-risk’ population and include the recommendation for
415 treatment of these dogs with anti-thrombotic therapy [10]. Despite the predisposition to
416 thromboembolic disease, the underlying cause of hypercoagulability in dogs with PLN is
417 incompletely understood. Antithrombin deficiency and increased platelet aggregation
418 secondary to hypoalbuminemia have been identified in dogs with nephrotic syndrome,
419 however plasma antithrombin activity, UPCR and serum albumin concentration are not
420 predictive of thromboembolic complications [28]. Updated CURATIVE guidelines
421 published in 2022 [9] expanded on the definition of populations at risk for thrombosis,
422 and included dogs with transvenous pacemakers. Recommendations were made that
423 antithrombotic therapy should be used in all dogs with pacemakers and prothrombotic
424 comorbidities and considered in every dog following transvenous pacemaker
425 implantation.

426 The majority of dogs in this study received treatment with anti-thrombotic drugs
427 after PLAT diagnosis, and resolution of the thrombus was seen in more than half of the
428 dogs that underwent follow-up echocardiography. However, some dogs died before
429 therapy could be initiated, and other dogs had resolution of the thrombus without anti-
430 thrombotic drugs. There is currently no consensus on treatment of PLAT in people or in
431 dogs. Therapeutic management described in people include anti-coagulation,
432 thrombectomy, thrombolysis and pacemaker lead extraction [17, 29-31], however
433 evidence-based guidance for clinicians is limited and is usually made on a case-by-case

basis. Intravenous administration of heparin followed by warfarin is often used as an initial therapy [31]. This is in contrast to the treatment of dogs in this study, with the majority of patients receiving only anti-thrombotic therapy rather than anti-coagulant therapy following PLAT diagnosis. This is likely due to warfarin falling out of favor for use in veterinary medicine, with recommendations to use the oral anti-coagulants (rivaroxaban, apixaban) [32]. Oral anti-coagulants have been shown to be successful in decreasing thrombus size in several dogs [21, 22]. Although no dogs in our study received thrombolytic medications or had interventional procedures, treatment with unfractionated heparin and local infusion of recombinant tissue-plasminogen activator as well as interventional procedures for balloon venoplasty have been previously described to be successful in treating pacemaker lead thrombosis and cranial vena cava syndrome in two dogs [23].

The clinical importance and outcome of dogs with PLAT was previously unknown. Our study identified that dogs with PLAT had significantly shorter survival times when compared to those without PLAT. Whether this difference was due to the presence of PLAT, or due to an underlying disease process causing a hypercoagulable state is unknown, however prompt diagnosis and treatment as well as screening for risk factors may help improve the outcome in these dogs. In the entire population 14 dogs died suddenly, including one dog that died following a cardiopulmonary arrest on the day of PLAT diagnosis, nine dogs died due to PTEs and one died due to an arterial hindlimb thromboembolism. However, it is unknown whether the PLAT was the cause of death in these dogs, particularly in the absence of necropsies being performed and because concurrent disease was common.

This study is the largest study looking at dogs with permanent pacemakers. As in previous studies, atrioventricular block and sick sinus syndrome were the most common indications for pacemaker implantation in our study [1-6, 8, 33, 34]. The patient population reported here was similar to previous studies, with older dogs [1-8, 34], a slight predominance of female dogs [1, 2, 4, 5, 8] and a large variety of breeds [1-5, 7, 8, 33, 34] being included. The proportion of dogs with concurrent cardiac disease [1, 2, 5, 7, 8] and CHF [1-3, 5-7] in our population is similar to that which has been reported in previous studies. One study [4] had a lower proportion of both concurrent cardiac disease and CHF, implying that although a bradyarrhythmia alone can cause CHF, the presence of underlying cardiac disease is an important determinant for the development of CHF in dogs with bradyarrhythmias.

The majority of publications focus on transvenous pacemaker implantation [2-4, 6, 7, 33, 34]. In our study 78/606 (12.9%) of pacemakers were epicardial, and in other studies epicardial pacemakers accounted for 11.7-32.7% [1, 5] of pacemakers placed. Based on our data, we can see that there are differences between centers as to whether epicardial pacemakers are used. This may reflect the availability of a surgeon to place the epicardial lead or the cardiologist's assessment of other patient factors. Small patient size, the need for abdominal surgery and concurrent dermatological disease have all been previously reported as reasons to place an epicardial lead system [8]. While these were also reported as reasons for choosing an epicardial lead system in our population, the most common reason reported in our study was the presence of protein losing conditions, with other reasons including the presence of a hypercoagulable state. The decision to place an epicardial pacemaker in these cases

was potentially due to the concern about these dogs developing PLAT. Although only proteinuria was associated with PLAT in our study, the small number of cases and the retrospective nature mean that we cannot say that other conditions that cause a hypercoagulable state do not predispose dogs to PLAT.

In our study, 50/606 (9.5%) of transvenous pacemakers were dual chamber but dual chamber pacemakers have represented 0% [2, 3, 7, 34], 0.7% [1], 2.7% [5], 4.8% [4], 48.1% [33] and 100% [6] of transvenous pacemakers placed in other studies. There were slightly more active fixation than passive fixation leads in this study which is similar to a previous study [2], although in another study it was approximately even [1]. These differences in single versus dual chamber and active versus passive fixation are likely to reflect clinician preference and the availability of pacing systems. Rates of complications in this study (102/606, 16.8%) were slightly lower than in many previous studies (25-82%) [1-4, 6-8, 33, 34], but higher than in one study (11.8%) [5]. This may simply reflect the variable definition of complication used in each study and that reporting of other complications was not the primary aim of this study.

Median survival time from pacemaker implantation in our study (approximately 30 months) was similar to that previously reported in other studies [1, 6-8, 33], although some studies report slightly shorter (median survival 14-22 months) [3, 34] or longer (median survival 35 months; 55-65% of dogs alive at 36 months) [2, 4, 5] survival times. As with previous studies, the majority of dogs with pacemakers in our study did not die due to the pacemaker or due to cardiac disease [1-5, 34], likely reflecting the older age and high levels of comorbidities of the population at pacemaker implantation. In our study, younger age at implantation was associated with a better outcome. Age has been

503 previously associated with outcomes in dogs with pacemakers [1, 2], although one of
504 these studies [2] reported that dogs that were middle aged at implantation lived longer
505 than young or older dogs. In this study and one other study [1] CHF was a negative
506 prognostic indicator, but this was not reported in another study [2]. As with a previous
507 study [7], the presence of a pacemaker-related complication in our study resulted in a
508 poorer outcome. Our study reported that the presence of comorbidities was associated
509 with a poorer outcome, and this is in agreement with another study that reported the
510 presence of concurrent cardiac disease was associated with a worse outcome [4].

511 This study has several limitations in addition to those reported above that should
512 be considered. The echocardiographic appearance of lead-attached thrombi and
513 endocarditis may be very similar and differentiation by echocardiographic means alone
514 is not possible, however a lack of clinical signs associated with endocarditis at the time
515 of thrombus diagnosis or during follow-up in our dogs makes endocarditis less likely.
516 Transthoracic echocardiography identified thrombi in 26/27 of dogs in our study but in
517 the other dog a large thrombus obstructing the cranial vena cava was only identified on
518 computed tomography. Three dogs had a suspected PTE and a PLAT was not
519 identified. Using alternative imaging modalities may therefore be beneficial in dogs in
520 which thrombotic disease is suspected without evidence of PLAT on echocardiography.
521 As it is a retrospective study, clinical data including screening for risk factors for
522 hypercoagulability was not available for all dogs and may have been more likely to be
523 performed in those considered ‘at risk’ by the clinician. Follow-up examinations
524 including the timing of rechecks and diagnostics performed, were not standardized
525 among the study dogs. As some dogs did not show clinical signs associated with their

PLAT, this may have led to an overall under diagnosis of silent PLAT. It may have also introduced bias as follow-up echocardiography may have been more likely to be recommended in dogs with known risk factors for thrombosis or clinical signs of thrombosis, increasing the likelihood of identifying PLAT in these dogs. We can therefore can only conclude an association between proteinuria and PLAT. Further prospective studies with standardized screening for risk factors, timing of follow-up echocardiography and treatment groups would be required to investigate this association further as well as optimal management strategies.

Conclusion

Pacemaker-lead-associated thrombosis is common on echocardiography in the short- and long-term follow-up period of dogs following permanent transvenous pacemaker lead implantation. In more than half of dogs, the thrombi are considered an incidental finding, however PLAT can cause significant morbidity in some dogs and is associated with reduced survival time from pacemaker implantation. Proteinuria at the time of pacemaker implant is associated with PLAT, and significant proteinuria at the time of thrombus diagnosis is a common finding. Anti-thrombotic medications are frequently prescribed when PLAT is diagnosed and, in some dogs, resolution of the thrombus can be identified at follow-up assessments. Based on our data, we recommend screening for proteinuria prior to pacemaker implantation and regular echocardiographic monitoring of patients with transvenous pacemakers. We would also recommend considering the use of anti-thrombotics in patients with transvenous pacemakers that are diagnosed with proteinuria.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Footnotes

[h] IBM® SPSS® Statistics for Windows Version 27, IBM Corp, Armonk, NY, USA

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645 Table 1: Population characteristics of whole population, and comparisons between the three groups. AV: atrioventricular;
646 CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio; LV FS: left ventricular fractional shortening; N/A: not
647 applicable; nLVIDd: end-diastolic left ventricular internal diameter normalized for body weight; SND: sinus node
648 dysfunction; SSS: sick sinus syndrome; TEG: thromboelastography; UPCR: urine protein:creatinine ratio; WHWT: West
649 Highland White Terrier.

	Whole population	**Group 1 (transvenous pacemaker with echocardiographic follow up)**	**Group 2 (transvenous pacemaker without echocardiographic follow up)**	**Group 3 (epicardial pacemaker)**	**P value**	**Post hoc comparison P value (Bonferroni correction applied)**
Number of dogs	606	260	268	78		
Age (years)	9.7 (7.1-11.7) (n=606)	9.3 (6.4-11.3) (n=260)	10.1 (8.0-12.0) (n=268)	8.9 (7.0-11.0) (n=78)	0.003	Group 1 vs 2: 0.011 Group 2 vs 3: 0.025

Sex					0.477	
Male	261 (43.1%)	113 (43.5%)	110 (41.0%)	38 (48.7%)		
Female	345 (56.9%)	147 (56.5%)	158 (59.0%)	40 (51.3%)		
Neuter status					0.403	
Neutered	526 (86.8%)	224 (86.2%)	237 (88.4%)	65 (83.3%)		
Entire	79 (13.0%)	36 (13.8%)	30 (11.2%)	13 (16.7%)		
Unknown	1 (0.2%)	0 (0.0%)	1 (0.4%)	0		
Breed (top 6)	Cross-breed 62 (10.2%) Labrador 54 (8.9%) Schnauzer 49 (8.1%) WHWT 48 (7.9%)	Labrador 32 (12.3%) Cross-breed 31 (11.9%) WHWT 20 (7.7%) Schnauzer 17 (6.5%) Cocker Spaniel 15 (5.8%)	Cross-breed 27 (10.1%) WHWT 25 (9.3%) Schnauzer 22 (8.2%) Labrador 17 (6.3%) Cocker Spaniel 15 (5.6%)	Schnauzer 10 (12.8%) Cocker Spaniel 7 (9.0%) Dachshund 7 (9.0%) Labrador 5 (6.4%)	0.058	

	Cocker Spaniel 37 (6.1%) Jack Russell Terrier 23 (4.0%)	Cavalier King Charles Spaniel 13 (5.0%)	Jack Russell Terrier 11 (4.1%)	Cross-breed 4 (5.1%) WHWT 3 (3.8%)		
Body weight (kg)	12.9 (7.9-24.8) (n=604)	16.1 (8.2-28.4) (n=260)	12.3 (7.9-22.1) (n=267)	10.1 (6.9-18.9) (n=77)	0.004	Group 1 vs 3: 0.004
Body condition score (/9)	5 (5-6) (n=549)	5 (5-6) (n=232)	5 (5-6) (n=247)	5 (4-6) (n=70)	0.377	
Comorbidities	458 (75.6%)	188 (72.3%)	211 (78.7%)	59 (75.6%)	0.229	
Rhythm diagnosis					0.007	[a] 0.005
AV block	430 (71.0%)	190 (73.0%)	189 (70.5%)	51 (65.4%)		[b] 0.017
Atrial standstill	21 (3.5%)	17 (6.5%) [a]	2 (0.7%) [b]	2 (2.6%)		
Sinus arrest	3 (0.5%)	2 (0.8%)	1 (0.4%)	0 (0.0%)		
SND/SSS	148 (24.4%)	49 (18.8%)	74 (27.6%)	25 (32.1%)		
Vagally mediated	4 (0.7%)	2 (0.8%)	2 (0.7%)	0 (0.0%)		

In CHF at implantation	58 (9.6%)	27 (10.4%)	28 (10.4%)	3 (3.8%)	0.184	
Underwent echo prior to implantation	594 (98.0%)	257 (98.8%)	260 (97.0%)	77 (98.7%)	0.286	
LA:Ao	1.45 (1.28-1.70) (n=567)	1.47 (1.30-1.76) (n=246)	1.42 (1.24-1.62) (n=251)	1.49 (1.36-1.73) (n=72)	0.014	Group 2 vs 3: 0.033
nLVIDd	1.65 (1.50-1.86) (n=567)	1.71 (1.52-1.90) (n=244)	1.63 (1.47-1.82) (n=253)	1.65 (1.51-1.84) (n=70)	0.043	Group 1 vs 2: 0.036
LV FS	46.5 (40.0-52.6) % (n=574)	46.6 (39.0-53.0) % (n=247)	46.2 (40.1-52.3) % (n=254)	46.0 (41.1-51.3) % (n=73)	0.953	
Right atrial size (compared to left atrial size)					0.657	
<50%	164 (27.1%)	70 (26.9%)	84 (31.3%)	10 (12.8%)		

50-100%	220 (36.3%)	108 (41.5%)	96 (35.8%)	16 (20.5%)		
>100%	15 (2.5%)	6 (2.3%)	8 (3.0%)	1 (1.3%)		
Unknown	207 (34.2%)	76 (29.2%)	80 (29.9%)	51 (65.4%)		
Right ventricular size (compared to left ventricular size)					0.465	
<50%	313 (51.7%)	150 (57.7%)	144 (53.7%)	19 (24.4%)		
50-100%	80 (13.2%)	31 (11.9%)	41 (15.3%)	8 (10.3%)		
>100%	5 (0.8%)	3 (1.2%)	2 (0.7%)	0 (0.0%)		
Unknown	208 (34.3%)	76 (29.2%)	81 (30.2%)	51 (65.4%)		
Albumin (g/L)	32.0 (29.0-36.0) (n=487)	32.0 (28.5-35.0) (n=200)	33.0 (30.0-37.0) (n=222)	32.0 (28.0-34.0) (n=65)	0.006	Group 1 vs 2: 0.018 Group 2 vs 3: 0.040
Hypoalbuminemia	41/491 (8.4%)	19/203 (9.4%)	15/223 (6.7%)	7/65 (10.8%)	0.464	

UPCR	0.38 (0.09-1.93) (n=143)	0.30 (0.08-1.94) (n=58)	0.23 (0.08-0.78) (n=53)	1.89 (0.21-4.76) (n=32)	0.002	Group 1 vs 3: 0.013 Group 2 vs 3: 0.001
Proteinuria	77/155 (49.7%)	29/60 (48.3%)	24/60 (40.0%)	24/35 (68.6%) [a]	0.026	[a] 0.033
TEG hypercoagulable	2/3 (66.7%)	2/3 (66.7%)	0	0	N/A	
Length of hospitalization (days)	3 (1-4) (n=596)	3 (1-4) (n=259)	2 (1-4) (n=265)	3 (3-4) (n=72)	<0.001	Group 1 vs 3: <0.001 Group 2 vs 3: <0.001

651 Table 2: Reason listed in the medical records for an epicardial lead system being
652 chosen. PLE: protein-losing enteropathy; PLN: protein-losing nephropathy; *included
653 four patients with suspected/confirmed hyperadrenocorticism, and one patient with each
654 of immune-mediated hemolytic anemia, splenic thrombus and diffuse spontaneous echo
655 contrast on echocardiography.

Reason epicardial system chosen	**Number (%)**
PLN/PLE	23 (29.5%)
Patient size/demeanour	16 (20.5%)
Dermatologic disease	8 (10.3%)
Suspected hypercoagulable state*	7 (9.0%)
Complications from previous pacemaker	6 (7.7%)
Need for concurrent surgery	6 (7.7%)
Concurrent disease	4 (5.1%)
Structural cardiac disease	2 (2.6%)
PLN and patient size	1 (1.3%)
PLN and dermatologic disease	1 (1.3%)
Suspected hypercoagulable state* and need for concurrent surgery	1 (1.3%)
Unknown	3 (3.8%)

656

Table 3: Details of the chambers paced and lead fixation type in patients with a transvenous pacemaker system.

Chamber paced and lead type	**Number (%)**	
Single chamber – active lead	294 (55.7%)	477 (90.3%)
Single chamber – passive lead	168 (31.8%)	
Single chamber – unknown lead fixation	15 (2.8%)	
Dual chamber – active atrial lead, active ventricular lead	14 (2.7%)	50 (9.5%)
Dual chamber – active atrial lead, passive ventricular lead	7 (1.3%)	
Dual chamber – passive atrial lead, active ventricular lead	13 (2.5%)	
Dual chamber – passive atrial lead, passive ventricular lead	16 (3.0%)	
Dual chamber – unknown lead fixation	0 (0.0%)	
Unknown number of chambers paced and unknown lead fixation	1 (0.2%)	1 (0.2%)

Table 4: Comparison of characteristics at pacemaker implantation between patients that did and did not develop pacemaker-lead-associated thrombosis. AV: atrioventricular; CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio; LV FS: left ventricular fractional shortening; N/A: not applicable; nLVIDd: end-diastolic left ventricular internal diameter normalized for body weight; SND: sinus node dysfunction; SSS: sick sinus syndrome; UPCR: urine protein:creatinine ratio; WHWT: West Highland White Terrier.

	Pacemaker-lead-associated thrombosis	**No pacemaker-lead-associated thrombosis**	**P value**
Number of dogs	27	233	
Center			0.077
Center 1	2 (7.4%)	22 (9.4%)	
Center 2	7 (25.9%)	28 (12.0%)	
Center 3	7 (25.9%)	40 (17.2%)	
Center 4	6 (22.2%)	31 (13.3%)	
Center 5	3 (11.1%)	40 (17.2%)	
Center 6	2 (7.4%)	52 (22.3%)	
Center 7	0 (0.0%)	20 (8.6%)	

Age (years)	8.9 (4.1-12.2)	9.4 (6.6-11.3)	0.677
Sex			0.153
Male	8 (29.6%)	105 (45.1%)	
Female	19 (70.4%)	128 (54.9%)	
Neuter status			0.553
Neutered	22 (81.5%)	202 (86.7%)	
Entire	5 (18.5%)	31 (13.3%)	
Breed (top 6)	WHWT 5 (18.5%) Cross-breed 4 (14.8%) Cocker spaniel 2 (7.4%) Jack Russell terrier 2 (7.4%) Dogue de Bordeaux 2 (7.4%) Yorkshire terrier 2 (7.4%)	Labrador 31 (13.3%) Cross-breed 27 (11.6%) Schnauzer 17 (7.3%) WHWT 15 (6.4%) Cocker spaniel 13 (5.6%) Cavalier King Charles Spaniel 12 (5.2%)	0.438
Body weight (kg)	10.2 (6.8-20.0)	17.0 (8.4-28.8)	0.071
Body condition score (/9)	5 (5-6) (n=24)	5 (5-6) (n=208)	0.779

Comorbidities	17 (63.0%)	171 (73.4%)	0.261
Rhythm diagnosis			0.950
AV block	19 (70.4%)	171 (73.4%)	
Atrial standstill	2 (7.4%)	15 (6.4%)	
Sinus arrest	0 (0.0%)	2 (0.9%)	
SND/SSS	6 (22.2%)	43 (18.5%)	
Vagally mediated	0 (0.0%)	2 (0.9%)	
In CHF	1 (3.7%)	26 (11.2%)	0.329
LA:Ao	1.49 (1.34-1.86) (n=25)	1.47 (1.30-1.73) (n=221)	0.444
nLVIDd	1.60 (1.40-1.84) (n=24)	1.72 (1.52-1.90) (n=220)	0.054
LV FS	52.5 (45.3-57.5) % (n=24)	46.3 (38.8-52.3) % (n=223)	0.010
Right atrial size (compared to left atrial size)			0.156
<50%	10 (37.0%)	60 (25.8%)	
50-100%	10 (27.0%)	98 (42.1%)	
>100%	2 (7.4%)	4 (1.7%)	

Unknown	5 (18.5%)	71 (30.5%)	
Right ventricular size (compared to left ventricular size)			0.805
<50%	18 (66.7%)	132 (56.7%)	
50-100%	4 (14.8%)	27 (11.6%)	
>100%	0 (0.0%)	3 (1.3%)	
Unknown	5 (18.5%)	71 (30.5%)	
Albumin (g/L)	29.0 (26.5-35.5) (n=17)	32.0 (29.0-35.0) (n=183)	0.082
Hypoalbuminemia	4/18 (22.2%)	15/185 (8.1%)	0.072
UPCR	2.38 (0.68-6.75) (n=6)	0.20 (0.06-1.63) (n=52)	0.022
Proteinuria	6/6 (100.0%)	21/52 (40.4%)	0.007
TEG hypercoagulable	0	2/3 (66.7%)	N/A
Single vs dual chamber			0.740
Single chamber	24 (88.9%)	210 (90.1%)	
Dual chamber	3 (11.1%)	23 (9.9%)	

Ventricular lead passive vs active			1.000
Passive	9 (33.3%)	78 (33.5%)	
Active	17 (63.0%)	151 (64.8%)	
Unknown	1 (3.7%)	4 (1.7%)	

665

Table 5: Median survival time for the overall population and comparisons in survival times (log-rank test) for different factors. AV: atrioventricular; CHF: congestive heart failure; LA:Ao: left atrial to aortic ratio; LV FS: left ventricular fractional shortening; nLVIDd: end-diastolic left ventricular internal diameter normalized for body weight; PLAT: pacemaker-lead-associated thrombosis; SND: sinus node dysfunction; SSS: sick sinus syndrome; UPCR: urine protein:creatinine ratio.

	n	Survival time	P value
Overall	600	907 days (0-2661 days)	
Center			0.091
Center 1	33	1,056 days (70-1,469 days)	
Center 2	52	817 days (0-2,286 days)	
Center 3	86	828 days (0-2,661 days)	
Center 4	123	972 days (0-2,658 days)	
Center 5	115	733 days (4-2,120 days)	
Center 6	141	1,090 days (0-2,282 days)	
Center 7	50	1,625 days (1-2,232 days)	
Age			<0.001
≤7.0 years	146	>2,661 days (0-2,661 days)	

7.1-9.6 years	150	828 days (0-2,472 days)	
9.7-11.6 years	151	865 days (0-2,186 days)	
≥11.7 years	153	696 days (2-2,450 days)	
Sex			0.100
Male	260	842 days (0-2,658 days)	
Female	340	907 days (0-2,661 days)	
Neuter status			0.029
Neutered	522	877 days (0-2,658 days)	
Entire	78	1,070 days (0-2,661 days)	
Body weight			0.937
≤7.8 kgs	147	936 days (0-2,661 days)	
7.9-12.8 kgs	150	909 days (0-2,450 days)	
12.9-24.6 kgs	150	841 days (0-2,472 days)	
≥24.7 kgs	150	949 days (0-2,658 days)	
Body condition score (/9)			<0.001
Underweight (≤3/9)	34	491 days (0-1,477 days)	

Ideal weight (4-5/9)	288	1,018 days (0-2,658 days)	
Overweight (≥6/9)	221	882 days (0-2,450 days)	
Comorbidities			<0.001
Yes	452	795 days (0-2,661 days)	
No	148	1,324 days (0-2,658 days)	
Rhythm diagnosis			0.533
AV block	426	949 days (0-2,658 days)	
Atrial standstill	21	653 days (0-1,988 days)	
Sinus arrest	3	>1,353 days (507-1,353 days)	
SND/SSS	146	801 days (0-2,661 days)	
Vagally mediated	4	603 days (68-1,054 days)	
In CHF at implantation			<0.001
Yes	55	551 days (0-1948 days)	
No	545	963 days (0-2,661 days)	
LA:Ao			0.009
≤1.28	143	842 days (0-2,658 days)	

1.29-1.45	140	1,194 days (2-2,232 days)	
1.46-1.69	139	1,102 days (1-2,661 days)	
≥1.70	141	797 days (0-2,472 days)	
nLVIDd			0.546
≤1.49	141	828 days (0-2.661 days)	
1.50-1.65	141	949 days (0-2,472 days)	
1.66-1.85	140	984 days (0-2,186 days)	
≥1.86	139	895 days (0-2,658 days)	
LV FS			0.608
≤40.0%	144	808 days (0-2,279 days)	
40.1-46.3%	139	1,018 days (0-2,472 days)	
46.4-52.4%	142	979 days (0-2,658 days)	
≥52.5%	143	842 days (1-2,661 days)	
Right atrial size (compared to left atrial size)			0.034
<50%	164	828 days (4-2,658 days)	
50-100%	219	1,033 days (0-2,661 days)	

>100%	15	386 days (0-1,650 days)	
Right ventricular size (compared to left ventricular size)			0.048
<50%	312	907 days (1-2,661 days)	
50-100%	80	777 days (0-2,450 days)	
>100%	5	461 days (0-505 days)	
Albumin (g/L)			0.054
≤28.9	109	801 days (0-1,922 days)	
29.0-31.9	98	801 days (0-2,661 days)	
32.0-34.9	121	826 days (1-2,472 days)	
≥35.0	154	1,142 days (0-2,658 days)	
Hypoalbuminemia			0.010
Yes	41	797 days (0-1,906 days)	
No	445	912 days (0-2,661 days)	
UPCR			0.337
≤0.10	37	941 days (0-2,279 days) days	
0.11-0.49	38	701 days (29-2,071 days)	

0.50-1.99	30	805 days (0-2,472 days)	
≥2.00	34	924 days (12-1,892 days)	
Proteinuria			0.625
Yes	76	801 days (0-2,472 days)	
No	75	865 days (0-2,279 days)	
Pacemaker			0.064
Transvenous	522	842 days (0-2,661 days)	
Epicardial	78	1,206 days (0-2,472 days)	
Single vs dual chamber			0.632
Single chamber	471	842 days (0-2,661 days)	
Dual chamber	50	1,018 days (4-2,120 days)	
Ventricular lead passive vs active			0.240
Passive	188	791 days (0-2,658 days)	
Active	318	907 days (0-2,661 days)	
Pacemaker complications			0.021
Yes	102	795 days (0-2,128 days)	

No	498	963 days (0-2,661 days)	
PLAT			0.003
Yes	27	677 days (9-1,988 days)	
No	232	1,105 days (1-2,661 days)	

670

671 Figure legends

672

673 Figure 1: Echocardiographic image of a pacemaker-associated-lead thrombosis. LA: left
674 atrium; RA: right atrium; *: pacemaker-associated-lead thrombosis.

675

676 Figure 2: Flow chart showing enrolment and grouping of dogs in the study.

677

678 Figure 3: Comorbidities in the population. Figure 3a: Comorbidities in the whole
679 population, divided by organ system. Figure 3b: Cardiac comorbidities in the whole
680 population. ARVC: arrhythmogenic right ventricular cardiomyopathy; MMVD:
681 myxomatous mitral valve disease: SPAVF: systemic to pulmonary arteriovenous fistula.

682

683 Figure 4: Percentage of dogs in groups 1, 2 and 3. Comparison of the percentages of
684 dogs in each group across the seven centers. *Statistically significant difference
685 compared to expected value.

686

687 Figure 5: Anti-thrombotic medications that the 27 dogs that developed pacemaker-lead-
688 associated thrombosis were receiving before and following their diagnosis. LMWH: low
689 molecular weight heparin.

690

691 Figure 6: Survival curve (all cause mortality): dogs that developed pacemaker-lead-
692 associated thrombosis had shorter survival times from pacemaker implantation (677
693 days (9-1,988 days)) than those that didn’t develop pacemaker-lead-associated
694 thrombosis (1,105 days (1-2,661 days)) (P=0.003).