Four-Year Follow-Up Persistent Atrial Standstill in a Dog

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ABSTRACT

This report describes a case of idiopathic permanent atrial standstill (PAS) with histopathological evidence of right atrial replacement fibrosis in a mixed-breed female dog that underwent echocardiographic and electrocardiographic follow-up examinations during 4 consecutive years, until its death from chronic renal and pre-renal azotemia. To the best of the authors' knowledge, this is the longest survival time reported in the veterinary literature of a dog with PAS that never received pacemaker therapy.

Keywords: Dog; Electrocardiogram; Idiopathic Permanent Atrial Standstill; Canine.

INTRODUCTION

Atrial standstill (also known as "silent atrium or atrial paralysis") is a disorder or the cardiac rhythm that involves the complete absence of electrical atrial activity and is defined as the total lack of auricular depolarization. Atrial standstill has been divided into three categories: temporary, terminal and persistent. (1, 2, 3).

Temporary atrial standstill is related mainly to hyperkalemia, the most frequent causes of which include an obstruction of the urinary tract in cats, or hypocorticism (Addison's syndrome) in dogs (4). Nevertheless, there are also sporadic reports of temporary silent atrium related to toxicity by quinidine or digitalis, myocardial injury secondary to hypoxia, or hypothermia (5). In all of these potentially transient situations, the heart returns to normal sinus rhythm (NSR) after resolution of the underlying causes.

Terminal atrial standstill develops secondary to some chronic cardiac pathologies (infective or other myocarditis) or to muscular dystrophies that affect cardiac and sometimes skeletal muscle, as has been reported in humans (5). It has also been reported sporadically in dogs, in conditions such as in congenital deficiency of dystrophin in the Golden retriever and the Rottweiler (6). Furthermore there is a report of a mixed-breed dog with to Nemaline myopathy and concomitant hypothyroidism (7).

The diagnosis of (idiopathic) persistent atrial standstill is based on the exclusion of abnormal serum concentrations of certain electrolytes, non-exposure to certain drug toxicities, hypothernmia, absence of skeletal muscular pathologies and any possible terminal condition (5). Electrocardiographic findings that are considered compatible with persistent atrial standstill, include a complete total absence of P waves on 6 limb leads at least, with no evidence of F waves of atrial fibrillation or flutter (8), the presence of a nodal or a ventricular escape rhythm, and a negative atropine test, all under normal concentrations of serum electrolytes (5).

Persistent atrial standstill has been sporadically reported in Siamese cats (9), and more commonly detected in dogs (10, 11). Its causes are still subject for debate but various physiopathological mechanisms have been proposed in human patients that include infiltration of the atrium by fibroblasts, inflammatory cells or amyloid; mutation (SCN5A) of a protein involved in the fetal development of the cardiac canal, or molecular defects of the protein Conexin 40 or the ryanodine receptor (10).

Clinical signs produced in atrial standstill might include right-sided congestive heart failure, along with signs of a decreased cardiac output such as fatigue, weakness, exercise intolerance, syncope, pallor, and hypothermia (11, 1, 7). These can be attributed to persistent bradycardia, the resultant decreased cardiac output which might be exacerbated by a less than ideal ventricular filling due to the lack of atrial contraction (2). In addition, some degree of ventricular diastolic dysfunction, chronic neurohormonal activation, and altered plasma levels of atrial natriuretic peptide (ANP) might be involved (5).

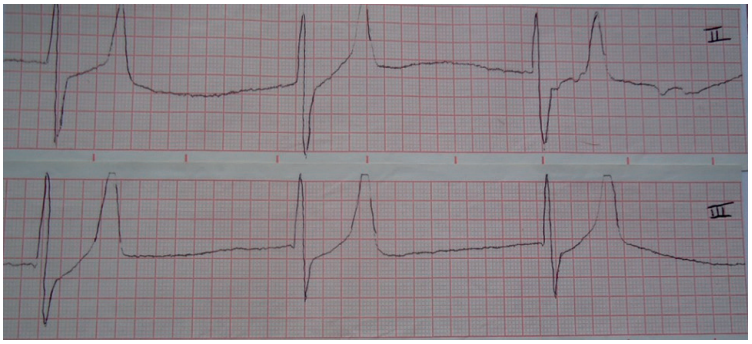

Figure 1: Surface Electrocardiogram, Leads II and III, paper speed 50mm/sec, sensitivity 1 cm/mV

The definitive treatment for persistent atrial standstill is the implantation of a pacemaker (10), which can completely reverse the clinical signs, especially if these are triggered by bradycardia. Retrospective studies (12) demonstrated that dogs with PAS have a median survival time of 866 days with pacemaker implantation, with a wide range of survival time observed. Another study also describes a survival times of 3-5 years after pacemaker implantation in two young Labrador retriever dogs with bradycardia-induced syncope resulting from atrial myopathy that were managed medically for approximately 7 years (13). One report (14) demonstrated that some dogs with persistent atrial standstill can survive for extended time periods.

In this study we describes a case of mixed-breed female dog with idiopathic permanent atrial standstill (PAS) with histopathological evidence of right atrial replacement fibrosis during 4 consecutive years, until its death from chronic renal and pre-renal azotemia.

MATERIALS AND METHODS

Case Report

In February 2011, a six year old mongrel female spayed Labrador retriever weighing 25.5 kg was brought to the Diego Villegas Toro Veterinary Hospital of the University of Caldas (Manizales – Colombia) with a clinical history of abdominal distension, muscle weakness and occasional syncope.

Physical examination revealed a poor body condition (BCS of 2/5), bradycardia of 62 beats per minute, pale mucous membranes and prominent abdominal distension. No jugular venous distention or hypothermia were recorded.

A complete blood count showed no abnormalities; liver transaminases were within normal reference range alanine aminotransferase (ALT) was 20 U/L (reference range: <85 U/L), asparate aminotransferase (AST) was 13 U/L (reference range: <90 U/L), serum potassium was 3.8 Meq/l (reference range: 3.5-5 Meq/l). Laboratory abnormalities were low serum albumin (18.9 g/L reference range: 26-40 g/L) associated probably with inadequate protein intake, which then normalized (37 g/L), azotemia with serum creatinine of 2.2 mg/dl (reference range 0.6-1.8 mg/dl) and a urine specific gravity of 1.040; therefore, classified azotemia as pre-renal (as in long-standing hypo-perfusion of the kidneys).

Abdominal ultrasound revealed the presence of peritoneal fluid (which was later found to consist of modified transudate) with no other abnormalities.

A surface electrocardiogram demonstrated a lack of P waves (leads I, II, III, AVr, AVL and AVf, no precordial unipolar leads were used) without evidence of F waves of atrial fibrillation or flutter (a slight oscillation of the baseline was attributed to tremors of the patient during the examination), accompanied by QRS waves with a normal R-wave amplitude at 1.9mV and an increased (110-120 ms) QRS duration, with a highly regular R-R interval reflecting a heart rate of up to 50 beats per minute compatible with either a nodal (junctional) escape rhythm with aberrant ventricular conduction (a bundle branch block) or with a ventricular escape rhythm (Figure1).

However, since fine baseline undulations were also recorded electrocardiographically, atrial fibrillation with concomitant complete atrioventricular block could not be definitively ruled out without using invasive, intra-cardiac electrophysiological testing. While a hyperkalemia-related sino-ventricular rhythm was definitively ruled out, sick si-

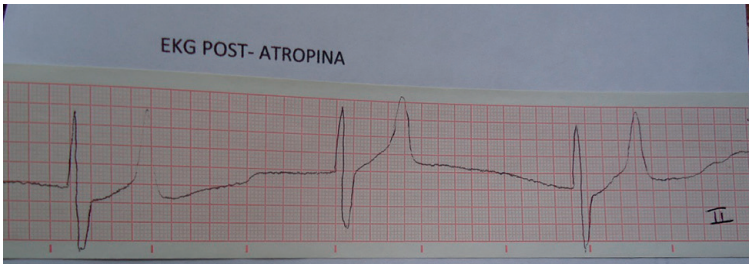

Figure 2: Surface electrocardiogram 30 minutes after subcutaneous atropine administration. Lead II, paper speed 50 mm/sec, sensitivity 1 cm/mV.

nus syndrome, sinus arrest, and sinus standstill are all rare differential diagnoses that could have also been considered in this case. Lastly, systemic lupus erythematosus as well as myasthenia gravis, which are described as possible underlying etiologies for persistent atrial standstill were also never ruled out.

Echocardiography (Mindray DP50, microconvex 6,5 MHz transducer) revealed atrial hypokinesia and pleural effusion, with no other abnormalities (see Table 1).

Next, an atropine test was performed, using a subcutaneous route at 0.04 mg/kg of atropine sulfate (zoo, Bogota, Colombia), followed by an electrocardiographic tracing 30 minutes later, in which no change was seen with respect to the previous ECG (Figure 2).

Based on clinical signs, the lack of P waves with a suspected ventricular escape rhythm, a null response to atropine, normal electrolyte levels, and the lack of a terminal condition, a persistent atrial standstill with secondary right-sided congestive heart failure was the working diagnosis, for which a prescription diet was advised (Hill's h/d; Hills Pet Nutrition, Kansas, USA). Exercise was to be limited to the minimum and drug treatment included enalapril (MK, Bogotá, Colombia) at 10 mg PO q12h and 80 mg PO q12h of furosemide (MK, Bogotá, Colombia). Any attempt to reduce the dose of furosemide caused a rapid recurrence of ascites and currently pimobendan has not been approved for our country. Pacemaker therapy was not an available or an affordable option.

The patient was serially monitored for four years during which appetite and activity levels were considered normal by the owner; however, some level of ascites as well as occasional syncope persisted. Tests of liver transaminases, plasma protein, serum electrolytes and complete blood counts were always within normal reference ranges.

Serum creatinine levels remained elevated, gradually progressing, and were always higher than the reference ranges, compatible with chronic pre-renal azotemia associated with the combination of chronically decreased cardiac output and the chronic use of high-dose diuretic therapy. This conclusion was based on the lack of proteinuria or hyperphosphatemia that would have otherwise suggested renal azotemia. BUN levels, total solids and PVC were stable until 2014 when they increased (BUN >335 mg/dl – reference range: 15-59 mg/dL, total solids 62 g/L – reference range: 55-75 g/L, and PVC 0.32 reference range: 0.37-0.55 L/L).

Urinary specific gravity was not considered useful as an evaluable parameter since isosthenuria persisted in this patient due to the persistent use of high dose diuretics.

In serial echocardiograms performed every six months following initial presentation, a gradual expansion of both atria chambers was observed (Figure 3), while ventricular dimensions and fractional shortening (Figure 4) remained constant throughout the disease course, showing only a slight increase in the final stages (Table 1).

Table 1: Evolution of echocardiographic and laboratory parameters during follow up visits over parameters 4 years post initial admission

	February 2011	June 2012	June 2013	June 2014	Reference value (15)
Left atrial diameter (systolic atrial width in long axis imaging B-mode a cross the LA body)	26.9 mm	35.8 mm	54.5mm	62.3mm	22.5-24.2mm
Right atrium diameter (systolic atrial width in long axis imaging)	22.6 mm	30.1 mm	38.3mm	87.6mm	
Ratio atrium/aorta (B-mode across the LA body)	1.29	1.72	2.62	2.99	1-1.2
Left ventricle diastole diameter (short axis M-mode)	40.5 mm	40.9 mm	41.5 mm	44.6 mm	37.7-40.5 mm
Shortening fraction	57.5%	55.2%	58%	49%	28-45%
Serum creatinine	2.2 mg/dl	2.3 mg/dl	3.2 mg/dl	3.9 mg/dl	0.6-1.8 mg/dl
Urine specific gravity	1.040	1.015	1.008	1.008	> 1.030
Serum potassium	3.8 mEq/l	4.1 mEq/l	4.6 mEq/l	3.9 mEq/l	3.5-5.5 mEq/L

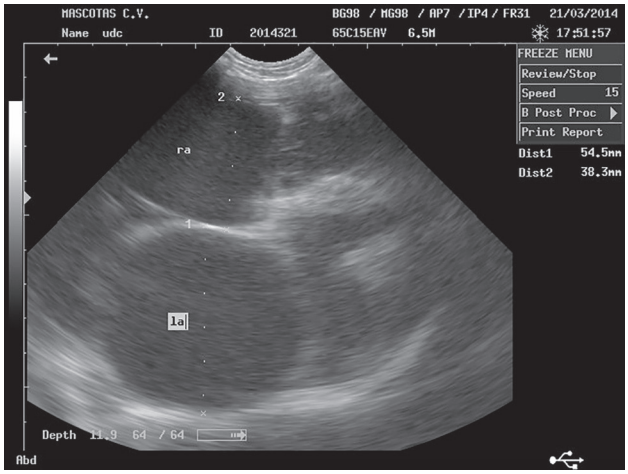

Figure 3: A right parasternal long axis view of the heart base echocardiographic image using a 6.5MHz transducer, revealing marked biatrial enlargement.

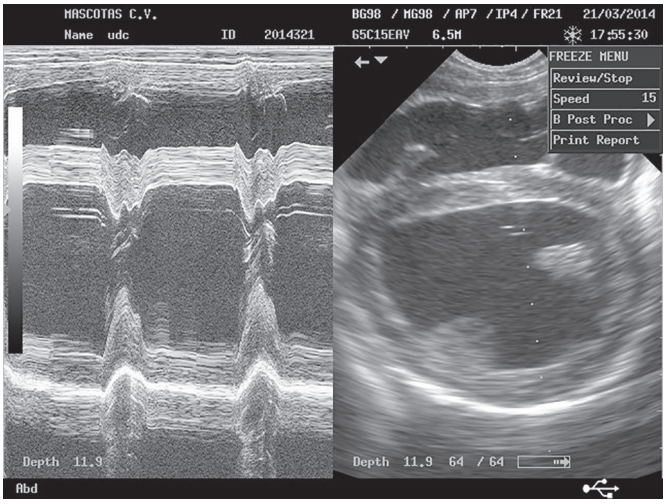

Figure 4: M-mode echocardiography at the right parasternal short axis view of the ventricles, displaying a hyperdynamic left ventricular contraction (FS>50%).

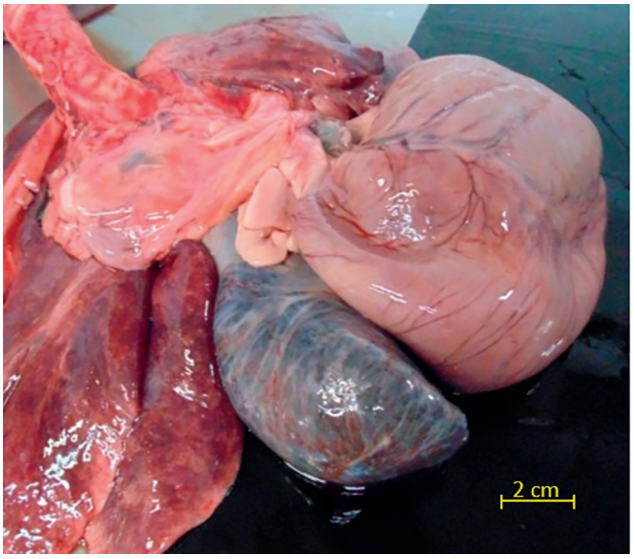

Figure 5: the image of heart and lung necropsy revealing severe right-sided atriomegaly.

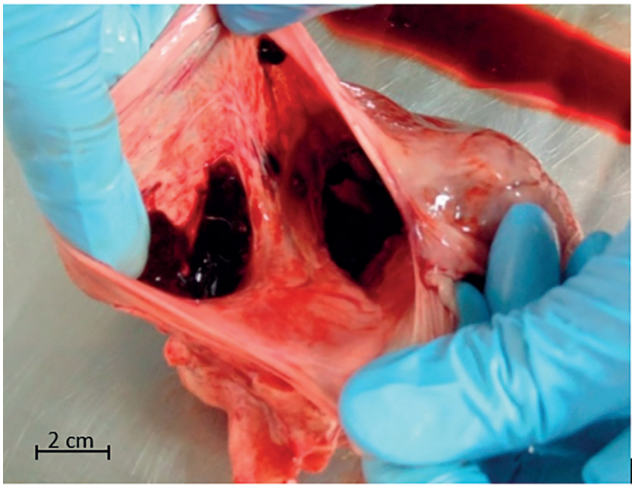

Figure 6: Internal image of the right atrium reveal enlargement. The wall thickness was not different from that of the other atrium.

Six months after diagnosis, and with a partial response to drug treatment, a pacemaker was suggested as a definitive treatment option for this patient, but was declined.

The patient died at home in August 2014, with signs that may suggest renal failure (vomiting, uremic breath, polydipsia and polyuria). Necropsy revealed severe right-sided atriomegaly with thinning of the right atrial walls (Figures 5 and 6). Slight bilateral nephromegaly was also observed. No other abnormal findings were reported.

Histopathology of the right atrium and kidneys (Figures 7, 8 and 9) demonstrated bilateral glomerulonephritis, an increased adipose tissue in the right atrial myocardium, at the expense of atrial myocytes, as in replacement fibrosis.

DISCUSSION

Atrial standstill is a rare condition in small animal medicine, and is typically secondary to other disease processes. The diagnostic procedure consisted of ruling out all possible primary alterations that may be causing this rare disturbance.

Occasionally, as seen in this particular case, this condition

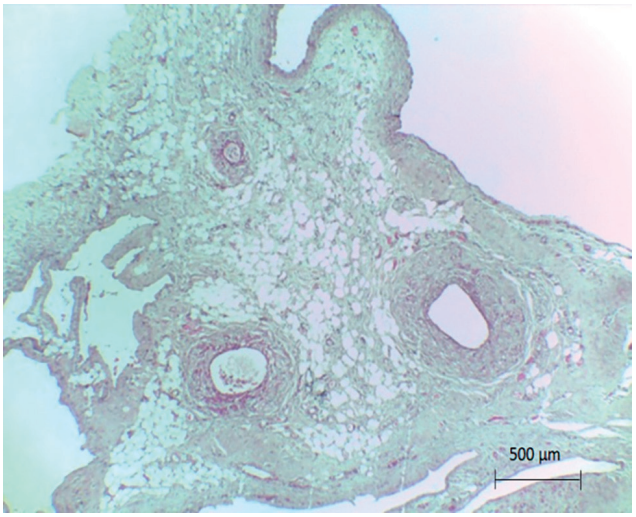

Figure 7: Microphotography of the right atrial myocardium at the level of the sinoatrial node. An endothelial coating is observed which is supported by a loose connective tissue in the inner portion that holds three blood vessels of large muscle layers (including nodal artery) and pericytes related to these structures and myocytes of the right atrium. A cut of nerve tissue is observed (component of the autonomic nervous system, cardiac pacemaker). (H&E stain, 4x)

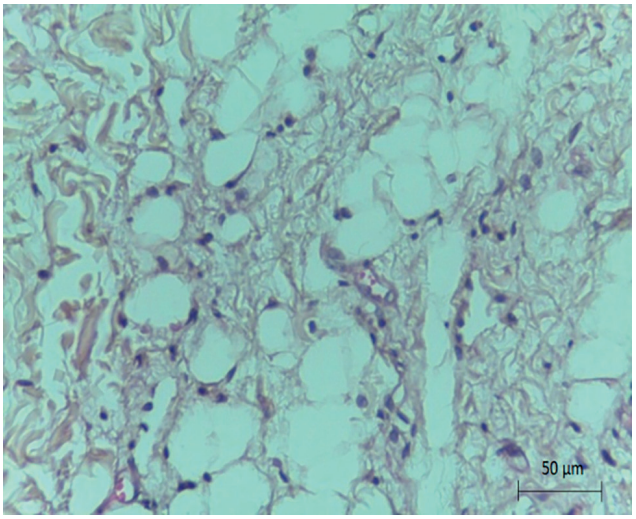

Figure 8: Microphotography, increase of the amount of adipose tissue in the right atrial myocardium. The histopathological findings of atrial myocardium revealed significant myocardial replacement by adipose tissue; however, there are no changes that may suggest myopathy. (H&E stain, 40x)

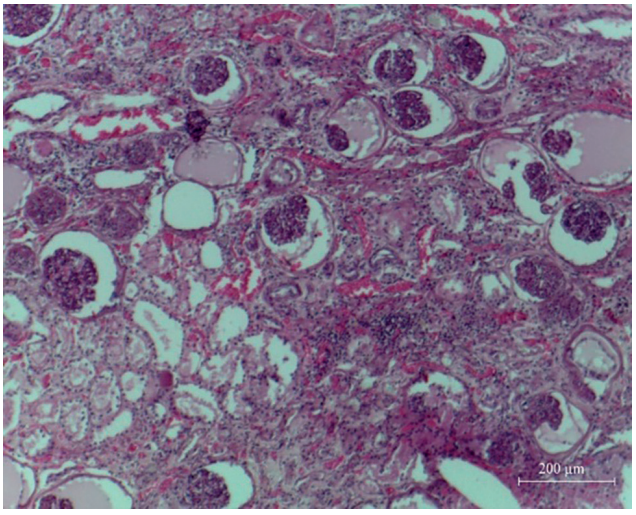

Figure 9: Microphotography of a kidney, severe multifocal glomerulonephritis. Note the inflammatory infiltrate. Extensive sclerosis (SC) (H&E stain, 10x). This was found in both kidneys. (H&E stain, 10x)

appeared to be primary and the challenge was to provide a reasonable quality of life for as long as practically possible.

The implantation of a pacemaker was the most appropriate and a definitive solution; however, in countries with low purchasing power such as Colombia, this alternative is unrealistic for the vast majority of patient owners, which necessitates adopting some other mitigating measures to achieve the above goals.

Survival rate less than 18 months has been reported (16) when a pacemaker is not implanted. However, the presently reported patient survived for 4 years, with tolerable clinical symptoms, and an acceptable quality of life. It is striking that the death of our patient was not apparently due to heart problems, but the low cardiac output sustained for long term led to the exacerbation of an underlying, primary kidney disease, which was the trigger of death. In retrospect, chronic, high dose diuretic therapy exacerbated the impact of the chronically decreased cardiac output which only worsened the already progressive primary glomerulonephritic process.

It is possible that in these patients a diuretic such as spironolactone may not cause progressive worsening of kidney function however its capacity for controlling edema formation is inferior to furosemide. Despite this, gradual weaning off or decreasing furosemide to a certain lower dose, in parallel to gradually increasing doses of spironolactone over two to three weeks, could have helped maintain a steady state in terms of effective diuretic control, while minimizing the risks involved with diuretic therapy inducing pre-renal azotemia, perhaps enough to not only to maintain a reasonable quality of life but also to prolong the patient's life even beyond the reported four years.

Another medication that could contribute with a benefit in these type of patients would be pimobendan to improve inotropism, however, it could not be used in this patient because at the time of the diagnosis the use of this medication was not authorized in our country.

In this case we found histopathological evidence of right atrial replacement fibrosis, without extensive and severe injury, necrosis or chronic active myocarditis of atrial muscle cells, different from those found in human literature (17). In the latter case of PAS, atrial fibrillation developed from an association with rheumatic combined valvular heart disease that showed histopathologic findings associated with moderated patchy lymphocyte and mononuclear cell infiltration with myocardial loss in the right atrium. In this human case the myocardium showed a loose appearance due to moderate, diffuse interstitial edema and fibrosis, suggesting an extensive and severe, but non-specific injury of atrial muscle cells that could induce persistent atrial standstill.

A case of PAS described in a 10-month-old dog with ascites as a presenting complaint showed multiple areas of atrial and ventricular myocardial necrosis and fibrosis, with chronic active myocarditis and obliteration of the SA and AV node and AV bundle (18).

This report describes a canine patient with suspected idiopathic permanent atrial standstill with histopathological evidence of right atrial replacement fibrosis that was followed through echocardiographic and electrocardiographic follow up examinations during 4 consecutive years, until its death from chronic renal and pre-renal azotemia. To the best of the authors' knowledge, this is the longest survival time reported in the veterinary literature of a dog with persistent atrial standstill that did no receive pacemaker therapy.

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