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Long-term management of high-grade atrioventricular block using cilostazol in a cat

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Abstract

Case summary A 12-year-old neutered female domestic shorthair cat was admitted for syncope. Clinical signs and electrocardiography revealed high-grade atrioventricular (AV) block. Treatment with cilostazol ameliorated the clinical signs and arrhythmia. However, the high-grade AV block recurred on several occasions. After 640 days, the cat presented again with clinical deterioration owing to reoccurrence of the arrhythmia and it died 11 days later. Histopathological examination revealed a loss of conduction cells within the His bundle.

Relevance and novel information To our knowledge, this is the first report of high-grade AV block treated with cilostazol in a cat. Treatment with cilostazol prolonged survival for 650 days without pacemaker implantation. Histological findings suggested that the AV block was related to fibrosis of the impulse conduction system.

Keywords: His bundle; cilostazol; electrocardiography; atrioventricular block

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Introduction

Atrioventricular (AV) block is a condition wherein conduction from the atria to the ventricles is delayed or blocked.[1] Using electrocardiography (ECG), AV blocks can be classified into first-, second- and third-degree blocks according to the degree of conduction disturbance. In second-degree AV block, an intermittent conduction disturbance develops between the atrium and ventricle, and low ventricular rates are observed vs atrial rates. Second-degree AV block with one QRS complex conduction for every ⩾3 P waves is defined as high-grade AV block.[2] Patients with second-degree AV block usually show no clinical signs; however, many patients with high-grade or third-degree AV block show clinical signs, such as collapse, lethargy and syncope.[2–4] In cats, relatively few cases of high-grade AV blocks have been reported.[5,6]

Cardiac pacemaker implantation is the preferred treatment in cats with symptomatic third-degree or high-grade AV block.[4,5,7] However, it requires a highly invasive procedure[7] and has been rarely reported in the literature.[8,9] Although a study has reported the use of terbutaline, a beta-adrenergic agonist, in a cat with high-grade AV block,[5] no drug therapy has been established for AV block.

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In human patients with advanced AV block, cilostazol has been administered before pacemaker implantation or in cases wherein pacemaker implantation is not possible.[10,11] Cilostazol is an antiplatelet aggregation agent with phosphodiesterase type-3 inhibitory effects.[11] It causes an increase in heart rate in human patients with bradycardic atrial fibrillation, sick sinus syndrome and second-degree AV block.[12,13] The mechanism for the increase in heart rate has not been fully elucidated to date; however, an increase in blood flow or intracellular cyclic adenosine monophosphate in the AV node tissue are speculated as the causes of this increase.[13] In human patients with third-degree AV block, cilostazol does not eliminate the AV conduction abnormality; however, it accelerates the rate of escape rhythm.[11] In addition, recovery of the AV conduction using cilostazol in a human patient with advanced AV block has been reported.[14]

The abovementioned evidence indicates that cilostazol can be used to treat bradyarrhythmia. Although, cilostazol has been reported to increase the heart rate in healthy dogs,[15] and successfully treat sick sinus syndrome in a dog, the use of cilostazol has not been reported in cats.[16] The present study describes the clinical course and histological findings in a cat with high-grade AV block treated with cilostazol.

Case description

A 12-year-old neutered female domestic shorthair cat with no previous significant clinical concerns was presented to our hospital with acute-onset intermittent syncope (day 1 of illness). The cat had been vaccinated against feline herpesvirus-1, feline calicivirus and feline panleukopenia virus. During the physical examination, auscultation did not reveal any abnormalities; however, the mucous membranes were pale. Blood biochemical analyses revealed decreased potassium (2.6 mEq/l; reference interval [RI] 3.1–5.0 mEq/l) and albumin (2.3 g/dl; RI 2.4–3.8 g/dl) concentrations and increased alanine aminotransferase (111 U/l; RI 18–108 U/l), blood glucose (302 mg/dl; RI 63–132 mg/dl) and troponin I (0.102 ng/ml; RI <0.02 ng/ml) concentrations. White blood cell count (13,300/µl; RI 5500–19,500/µl), urea nitrogen (30.3 mg/dl; RI 17.6–32.8 mg/dl), creatinine (1.0 mg/dl; RI 0.8–1.8 mg/dl) and thyroxine (1.8 µg/dl; RI 0.6–3.9 µg/dl) were within the RIs. Radiographs revealed mild cardiomegaly (vertebral heart scale, 8.4; normal cats: 7.5 ± 0.3),[17] with no abnormalities identified in the lung field.

ECG at the first visit showed P waves without QRS complexes for approximately 20 s, followed by a normal sinus rhythm (Figure 1a). Syncope developed and was consistent with the absence of the QRS complex. This syncope occurred repeatedly approximately every 5 mins along with a spontaneous recovery cycle. Echo cardiography revealed diastolic regurgitation originating from the mitral valve to the left atrium when the QRS complex disappeared on the ECG. However, diastolic regurgitation was not observed in any valve in the systolic and diastolic phases when normal AV conduction was maintained. There was no hypertrophy or thinning of the myocardium or morphological abnormalities in the cardiac chambers, valves, aorta or pulmonary artery, and the rest of ECG was unremarkable. The left ventricular fractional shortening was 51.5%. Based on these findings, high-grade AV block without underlying structural heart disease was diagnosed.

Table 1 presents a chronological summary of body weight, vital signs, clinical signs and treatment. On day 1, the cat was maintained in a 40% oxygen atmosphere and received dobutamine (8 µg/kg/min, dobutamine hydrochloride injection; Koa Isei) and atropine (0.05 mg/kg, atropine sulfate injection; Mitsubishi Tanabe Pharma) intravenously and cilostazol (8 mg/kg q12h; Pletal, Otsuka Pharmaceutical) orally. On day 2, the cat was eupnoeic in room air and there was no syncope. Each of the P waves was associated with QRS complexes; however, ECG revealed wide QRS complexes (QRS interval: 60 ms) (Figure 1b). The cat regained activity and appetite, and was discharged thereafter. Blood glucose (128 mg/dl) was within the RI. The owner declined pacemaker implantation. The cat continued to receive cilostazol (8 mg/kg q12h, increased to 10 mg/kg q12h later) orally. On day 147, ECG revealed a normal sinus rhythm (Figure 1c), and the cat showed no clinical signs that were potentially referable to a bradyarrhythmia.

On day 403, the cat became lethargic and anorexic, and intermittent syncope developed. Over a long period of time during ECG examination, P waves were observed, whereas QRS complexes were absent, which were suggestive of a high-grade AV block (Figure 1d). ECG revealed normal sinus rhythm followed by a period without any ventricular escape activity (approximately 20 s). The cat received aminophylline (7 mg/kg q12h neophyllin; Eisai Co.) orally in addition to cilostazol. After this treatment, the cat's activity and appetite returned to normal and no syncope occurred. A normal sinus rhythm was observed during ECG on day 428 (Figure 1e).

On day 538, the cat revisited the hospital because of occasional collapse, but its activity and appetite remained normal. ECG revealed normal sinus rhythm followed by unconducted P waves, which were suggestive of high-grade AV block. A maximum of nine P waves were blocked for approximately 3 s. Ventricular escape rhythm with wide QRS complexes (QRS interval 73 ms) was observed during the loss of AV conduction (Figure 1f). ECG revealed mild mitral and tricuspid regurgitations during systole. The left ventricular fractional shortening was 51.5%.

On day 640, the cat became lethargic and anorexic again, and showed increased frequency of syncope. ECG revealed tachycardia (230 bpm) with low-amplitude QRS complexes and inverted T waves, followed by

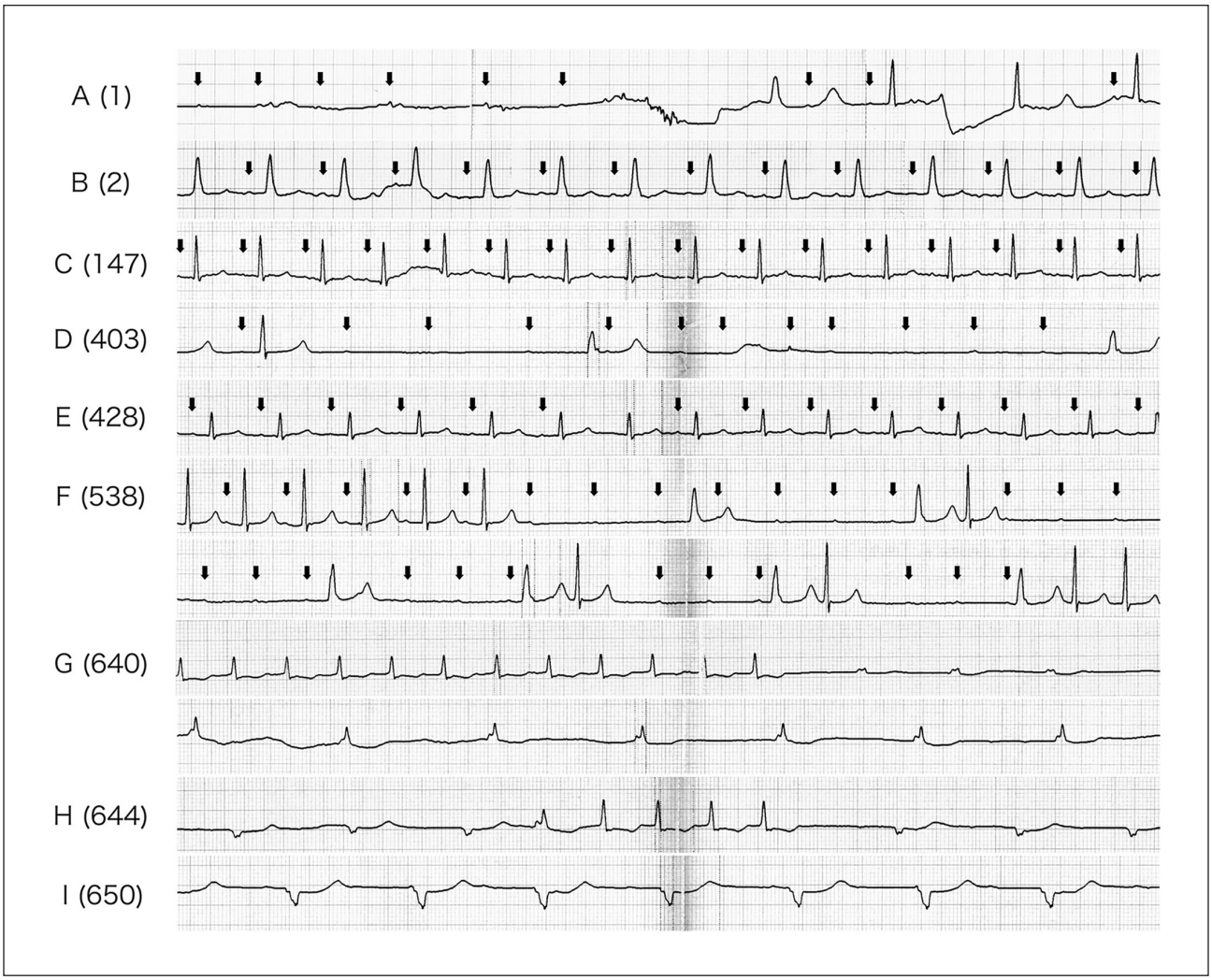

Figure 1 Lead II electrocardiogram. Days of illness are indicated in parentheses (10 mm/mV, 50 mm/s). Arrows indicate P waves

regular biphasic wide R waves at a slow rate (75 bpm; Figure 1g). The ECG waves observed later suggested ventricular escape rhythms. For treatment, in addition to the administration of cilostazol and aminophylline, isoproterenol (0.8 mg/kg q12h Proternol S; Kowa Co.) and isosorbide dinitrate (1 mg/kg q12h Frandol; Astellas Pharma) were orally administered. However, this treatment failed to improve the clinical signs, and the patient presented with dyspnoea on day 644. Ultrasonography revealed pleural effusion and ascites. Auscultation revealed a grade 2/6 systolic left apical murmur. ECG revealed positive or negative biphasic wide R waves, and normal sinus rhythm intermittently appeared (Figure 1h). ECG also revealed slight mitral and tricuspid regurgitations, enlargement of the left and right atria, and flattening of the interventricular septum. The left ventricular fractional shortening was 37.7%. The cat was maintained in a 40% oxygen atmosphere and received intravenous furosemide (1 mg/kg/6 h Lasix injection; Sanofi), followed by thoracocentesis.

On day 650, the cat became unconscious. Ventricular rhythms without clear P waves were observed during ECG (Figure 1i). The cat arrested on day 651.

Necropsy revealed enlarged right and left atria, but normal valves and myocardium. The liver was congested but the macroscopic examinations revealed no abnormality otherwise. Histopathological examinations of the heart revealed no abnormality of conducting cells in the AV node (Figure 2a) and the proximal part of the penetrating His bundle (Figure 2b). However, a remarkable decrease was observed in the number of conducting cells between the middle part of the penetrating His bundle (Figure 2c) and the proximal part of the bifurcating His bundle (Figure 2d). The lesion was partly or completely devoid of conducting cells and was replaced by immature fibrous tissues. Severe fibrosis was also observed in the basal part of the central fibrous body and crest of the ventricular septum. There was no abnormality in the sinus node, sinoatrial conduction path, distal part of the bifurcation of the His bundle, or left and right bundle branches.

Table 1 Chronological summary of body weight, vital signs, clinical signs and treatments in a cat with high-grade atrioventricular block

Day	Body weight (kg)	Body temperature (°C)	Respiratory rate (breaths/min)	Heart rate (beats/min)	Clinical signs	Treatment
1	2.95	36.7	78	45	Syncope and collapse	Atropine (0.05 mg/kg IV), dobutamine (8 µg/kg/min IV), oxygen therapy, cilostazol (8 mg/kg PO)
2	2.95	36.7	42	183	No syncope	Cilostazol (8 mg/kg PO)
100	2.75	38.3	48	160	No syncope	Cilostazol (10 mg/kg PO)
147	2.95	38.6	42	191	No syncope	Cilostazol (10 mg/kg PO)
165	2.9	38.0	42	184	No syncope	Cilostazol (10 mg/kg PO)
189	2.96	38.1	48	195	No syncope	Cilostazol (10 mg/kg PO)
238	3.05	38.4	48	210	No syncope	Cilostazol (10 mg/kg PO)
403	2.9	37.8	60	28	Occasional syncope	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO)
428	2.85	38.0	48	178	No syncope	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO)
452	2.8	38.4	42	181	No syncope	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO)
538	2.9	38.1	42	105	Occasional collapse	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO)
640	2.9	38.0	50	83	Syncope and collapse	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO), isoproterenol (0.8 mg/kg PO), isosorbide dinitrate (1 mg/kg PO)
644	2.85	38.5	54	30	Syncope, dyspnoea, pleural effusion and ascites	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO), furosemide (1 mg/kg/6 h IV), oxygen therapy
646	2.85	37.9	58	144	Syncope, dyspnoea, pleural effusion and ascites	Cilostazol (10 mg/kg PO), aminophylline (7 mg/kg PO), furosemide (1 mg/kg/6 h IV), oxygen therapy
650	1.9	35.0	54	83	Unconscious, dyspnoea, pleural effusion and ascites	Furosemide (1 mg/kg/6 h IV), oxygen therapy, removal of effusion

All oral administrations were given twice a day

Discussion

In veterinary medicine, syncope can be caused by structural cardiac diseases, arrhythmias and non-cardiac causes (eg, drug-induced, neurological diseases and metabolic disturbances).[3] High-grade and third-degree AV blocks are bradyarrhythmias that can cause syncope in cats.[4,5] In the present study, the cat was diagnosed with high-grade AV block at the first visit on the basis of the unconducted P waves followed by a normal sinus rhythm. The loss of AV conduction and syncope synchronously developed, thus confirming that the clinical signs had been caused by bradycardia and cerebral hypoperfusion due to the high-grade AV block.

Medical treatment for AV block has not been established in cats. In the present paper, the cat was treated using cilostazol and other drugs upon the owner's request. As shown in our report, cilostazol was effective during the initial cardiac treatment, as demonstrated by a significant increase in heart rate and amelioration of the syncope. Kellum and Stepien[4] reported the successful treatment of 14 cats with AV block using drug therapy, with a median survival period of 386 days. In the present report, the cat remained stable until approximately day 540, suggesting the efficacy of cilostazol as a choice of treatment for high-grade AV block in cats. However, the cat in our paper received aminophylline in addition to cilostazol from day 403 because it has been shown to improve AV conduction in human patients with AV block.[18] Therefore, the effect of drug therapy after day 403 should be evaluated considering the dual use of cilostazol and aminophylline. In our report, only a ventricular rhythm was observed during ECG after day

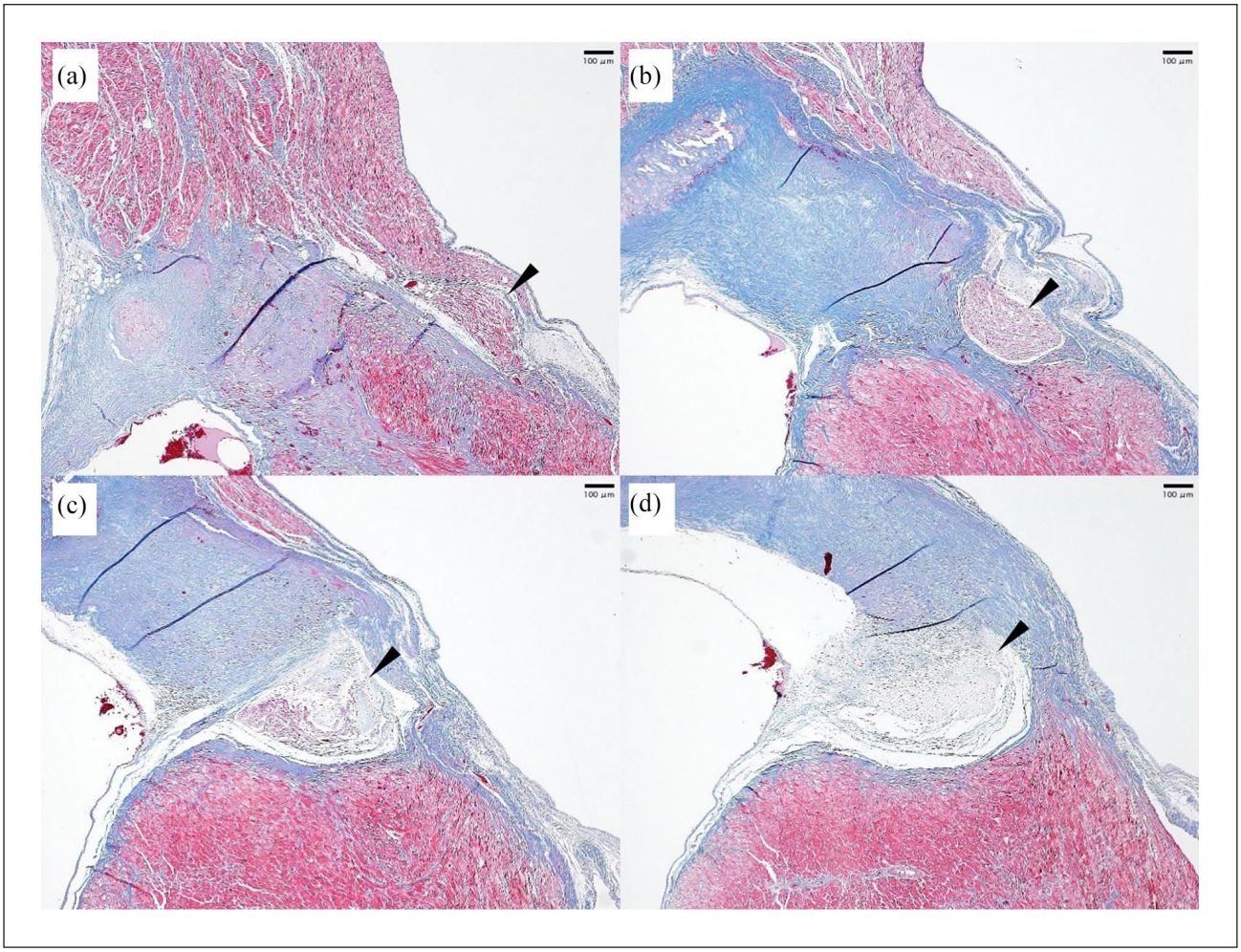

Figure 2 Histology of the horizontal section between the atrioventricular node and the His bundle (haematoxylin and eosin stain): (a) the AV node (arrowhead); (b) the proximal part of the penetrating His bundle (arrowhead); (c) the middle part of the penetrating His bundle (arrowhead); and (d) the proximal part of the bifurcating His bundle (arrowhead). Scale bar = 100 μm

650, which suggests that the condition progressed from partial to complete AV block. Although the cat's life could have been prolonged by implanting a heart pacemaker, the owner declined a pacemaker implantation.

In cats, abnormality in the impulse conduction system has been associated with cardiac diseases, such as hypertrophic cardiomyopathy, and systemic illness, such as hyperthyroidism.[19–22] The histological examination of 63 cats with cardiomyopathy revealed fibrosis in both the myocardium and the impulse conduction system.[22] In the present report, the lesion was found to be restricted to the impulse conduction system, and no abnormalities were identified in the myocardium. However, the presence of myocardial injury could not be excluded because blood troponin I concentration was increased. Non-cardiac diseases, such as azotaemia[23] or systemic inflammation,[24] increase blood troponin I concentrations in dogs; however, the cat in our study neither had azotaemia nor any clinical signs of systemic inflammation, with a white blood cell count within the RI. Dogs with second- or third-degree AV block may have increased blood troponin I concentration owing to acute or chronic myocarditis.[25] In addition, cats with transient trifascicular block with increased troponin I concentrations have been suspected to have myocarditis.[26] Moreover, the presence of myocarditis before necropsy was performed could not be excluded in the case reported in our paper; however, the histological examination did not reveal any findings suggestive of myocarditis. In humans, age-related idiopathic fibrosis, which is referred to as sclerosis of the left side of the cardiac skeleton, is considered as a common cause of complete AV block.[1] The advanced fibrosis observed in the present report was similar to the pathological change associated with sclerosis of the left side of the cardiac skeleton in humans.

The degeneration of cells in the His bundle poses a risk of progression to complete AV block.[1,19] Furthermore, in the present study, progression to complete AV block was suspected on day 650, which was confirmed by the histopathological findings showing a complete discontinuity

in the impulse conduction system. The lack of a clear P wave after day 640 possibly suggests sinus arrest; however, this seems unlikely because no abnormalities were observed in the sinus node or sinoatrial conduction path in the histopathological examinations.

A limitation of the present study is the lack of an ambulatory ECG monitoring system. Because transient abnormality can be undocumented by a conventional ECG, an ambulatory ECG could have evaluated the conduction abnormality more precisely, particularly when the cat showed no clinical signs.

Conclusions

To the best of our knowledge, this is the first report of the treatment of high-grade AV block using cilostazol in a cat. The use of cilostazol provided 650 days of survival without a pacemaker implantation. The histological findings suggested that the AV block was related to the fibrosis of the impulse conduction system in the cat.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animal(s) only (owned or unowned), and followed established internationally recognised high standards ('best practice') of individual veterinary clinical patient care. Ethical approval from a committee was not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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