

A combination of hyoscyamine and theophylline for treatment of sick sinus syndrome in a dog

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Abstract

A 12-year-old female West Highland White Terrier presented with a history of cardiac syncope. Physical examination revealed bradycardia. Sick sinus syndrome (SSS) was diagnosed with electrocardiography and 24-hour Holter monitoring. However, the owner made the decision to receive the pharmacological therapy. Therefore, a combination of hyoscyamine sulfate and theophylline was prescribed. Following two adjustments of drug dosage and frequency within a year, the total number of heartbeats increased from 58,091 to 73,686 beats, and the mean heart rate increased from 44 to 59 bpm. After the treatment, the dog became stable and no syncopal episodes were detected, despite the presence of supraventricular and ventricular tachycardias. In conclusion, a combination of hyoscyamine sulfate and theophylline can be considered an alternative treatment in dogs with SSS.

Keywords: bradycardia, hyoscyamine sulfate, sick sinus syndrome, syncope, theophylline

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Introduction

Sick sinus syndrome (SSS), also known as sinus node dysfunction (SND) is a disorder of the conduction system especially the sinoatrial node, characterized by a variety of arrhythmias including bradycardia, bradycardia-tachycardia syndrome, intermittent sinoatrial and atrioventricular blocks (AVBs), and sinus arrest. The causes are usually unknown but may involve idiopathic degeneration of the conduction system (Kraus and Gelzer, 2016). Dogs with SSS show both abnormal sinus node activity on electrocardiogram (ECG) and referable clinical signs such as weakness, ataxia, and syncope. Inadequate cardiac output and poor perfusion to vital organs including the brain are the main causes of overt clinical signs. In a retrospective review of 93 dogs defined with SSS and SND had been shown that the average age at the time of diagnosis was 11 ± 3 years (Ward *et al.*, 2016). Major risk factors included female sex and breeds such as West Highland White Terriers, Cocker Spaniels, Pugs, Dachshunds, and Miniature Schnauzers frequently predisposed (Saunders, 2005). In Europe, a study demonstrated a high incidence of SSS in Miniature Schnauzers, with patients presenting at a mean age of 10 ± 3.5 years and females slightly outnumbering males (57% vs. 43%) (Wess *et al.*, 2006). Isolated cases have also been documented in Bull Terriers (Kavanagh, 2002), Maltese (Park *et al.*, 2005), and Boxers (Burrage, 2012). The electrical abnormalities of SSS may result from failure of impulse generation, sinoatrial exit block, or other conduction disturbances within the surrounding atrial myocardium. The ECG was commonly used to identify various rhythm abnormalities secondary to disorders of sinus node or sino-atrial conduction. These abnormalities include sinus arrest longer than 4–6 seconds, prolonged sinus bradycardia with the mean heart rate less than 60 beats per minute (bpm), periodic AVBs, narrow-QRS complex tachycardia, and escape beats following period of sinus paused (Willis *et al.*, 2018). The treatment of choice for SSS is the implantation of a pacemaker device. However, positive chronotropic drugs such as theophylline, propantheline, hyoscyamine sulfate, or terbutaline can be used as alternative treatments for SSS in dogs (Adán and Crown, 2003).

Case Description

A 12-year-old female West Highland White Terrier, weighing 7.7 kg was present with 3 episodes of syncope over 2 days during running and barking. Each episode lasted approximately 20 seconds, and the dog recovered rapidly to normal. The syncopal episodes were classified as Type B with rigidity extremities and opisthotonus. Physical examination revealed bradyarrhythmia with normal heart and lung sounds. Her mucous membrane was pink, and the capillary refill time was less than 2 seconds. The rectal temperature was 100.4°F with normal hydration status. Blood samples were collected to analyze hematology (IDEXX ProCyte Dx™, Westbrook, USA), serum

chemistry (Dirui CS-300, Changchun, China), cortisol and TSH (Vcheck V200, Hwaseong-si, South Korea), T4 (IDEXX Catalyst One™, Westbrook, USA), electrolytes (Fuji Dri-Chem NX500i, Hanamaki, Japan), and cardiac troponin I (Abbott Alinity i, Irving, USA). Mild elevation of alkaline phosphatase (191 U/L, Table 1) was noted, whereas other parameters were within normal limits. Thoracic radiographs of both lateral and ventrodorsal planes were performed with the radiographic machine (Vet iRayDR, Shanghai, China). The images revealed a normal cardiac silhouette with a vertebral heart score (VHS) of 9.5 and normal lung parenchyma (Fig. 1).

The in-hospital ECG demonstrated sinus bradycardia with a heart rate of 60 bpm. However, no sinus pauses were observed during the 5-minute ECG recording, likely because of the intermittent nature of the arrhythmia. The atropine challenge test was performed at a dose of 0.04 mg/kg subcutaneously, yielding a peak heart rate of 140 bpm. Echocardiography was performed in both right and left lateral recumbencies with simultaneous ECG leads attached, using an ultrasound machine (Mindray DC 70 X-Insight, 4.0–10.0 MHz phased array transducer, Shenzhen, China). Trivial pulmonary valve insufficiency and intermittent sinus pauses were found. The left ventricular fractional shortening (41%) was within a normal limit. Abdominal ultrasonography revealed 60% of sediment in the gall bladder, small cysts in the right kidney, and the small liver estimated from the retraction of the liver within the cranial abdomen.

The first Holter monitoring test was performed for further diagnosis. ECG electrodes were attached to the thorax of the dog using three chest leads, which were connected to the Holter device (Fukuda Denshi Co., Ltd., Tokyo, Japan). After 24 hours, the device was removed and the ECG data was analyzed using commercial software (SCM-510, Fukuda Denshi Co., Ltd., Tokyo, Japan). During the Holter monitoring period, a total of 58,091 heartbeats were recorded, with a mean heart rate of 44 bpm (19–136 bpm) were reported (Fig. 2A). The 24-hour ECG tracings demonstrated 36 episodes of sinus arrest lasting greater than 6 seconds and alternating bradycardia-tachycardia patterns (Fig. 2B). High-grade AVBs occurred concomitantly with underlying sinus rhythm, junctional escape beats, or supraventricular tachycardias. Holter monitoring identified a total of 41 ventricular ectopic events, comprising 38 isolated ventricular premature complexes (VPCs), 1 ventricular couplet, and 2 episodes of ventricular bigeminy. Several episodes of paroxysmal supraventricular tachycardia were also recorded, with a maximum heart rate of 136 bpm during hospitalization, particularly when the dog was barking or agitation. The owner reported intermittent episodes of sudden weakness, tremors, and incoordination associated with periods of excitement or agitation; however, no syncope had been observed. Based on the clinical signs and findings from ECG and 24-hour Holter monitoring, the dog was diagnosed with SSS.

Table 1 Hematology, serum biochemistry, serum electrolyte, thyroid function tests, basal cortisol and cTnI values measured before drugs administration.

Parameters	Values	References	Parameters	Values	References
Red blood cell	8.27	5.65-8.87 × 10 ⁶ /μL	ALT	22	3-50 U/L
Hematocrit	52.4	34.3-61.7%	ALP	191	20-155 U/L
Hemoglobin	18.4	13.1-20.5 g/dL	Creatinine	0.89	0.5-1.5 mg/dL
MCV	63.4	61.6-73.5 fL	Blood urea nitrogen	9.9	4.5-30.5 mg/dL
MCH	22.2	21.2-25.9 pg	Albumin	3.2	2.3-4.1 g/dL
MCHC	35.1	32.0-37.9 g/dL	Total protein	6.5	4.8-6.6 g/dL
RDW	18.9	13.6-21.7%	Glucose	111	64-147 mg/dL
Platelets	420	148-484 × 10 ³ /μL	Total bilirubin	0.1	0.1-0.5 mg/dL
White blood cell	6.54	5.05-16.76 × 10 ³ /μL	Potassium	4.8	3.5-5.8 mmol/L
Neutrophil	3.86	2.95-11.64 × 10 ³ /μL	Sodium	159	144-160 mmol/L
Lymphocyte	1.35	1.05-5.10 × 10 ³ /μL	Chloride	118	109-122 mmol/L
Monocyte	1.09	0.16-1.12 × 10 ³ /μL	TT4	3.8	1.0-4.0 μg/dL
Eosinophil	0.22	0.06-1.23 × 10 ³ /μL	TSH	0.61	< 0.5 ng/mL
Basophil	0.02	0.00-0.10 × 10 ³ /μL	Basal cortisol	5.36	2-6 μg/dL
			cTnI	0.035	< 0.15 ng/mL

MCV, mean corpuscular volume MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TT4, total thyroxine; TSH, thyroid-stimulating hormone; cTnI, cardiac troponin I. References obtained from the Laboratory unit, Charoensuk Animal Hospital.

In this case, the owner requested pharmacological therapy rather than pacemaker therapy. Hyoscyamine sulfate (0.004 mg/kg PO q8h) and theophylline (8 mg/kg PO q12h) were initially prescribed. The dog's clinical response and any potential adverse effects were closely monitored throughout treatment. After two weeks, the 5-min ECG was re-evaluated and revealed both sinus rhythm and supraventricular arrhythmia with heart rates between 120–150 bpm (Fig. 3). These drug dosages were continued on the following hospital visits. Regular ECGs were performed every 2 months as routine checkups. After a 9-month period of these treatments, the dog started having mild incoordination, with the sinus tachycardia (240 bpm) presented on the 5-min ECG (Fig. 4). Therefore, hyoscyamine sulfate was adjusted from 0.004 mg/kg q8h to 0.004 mg/kg q12h. Three months following the medication adjustment, clinical signs persisted, and a 5-minute ECG revealed persistent sinus tachycardia at 220 bpm (Fig. 5). Subsequent dosage modifications to theophylline (8 mg/kg PO q24h) and hyoscyamine sulfate (0.004 mg/kg PO q8h) yielded complete resolution of the clinical signs.

Following one year of clinical stability, an annual electrocardiographic evaluation was performed (Fig. 6). Holter monitoring over 24 hours recorded a total of 73,686 heartbeats, with an increased mean heart rate of

59 bpm (minimum: 27 bpm; maximum: 200 bpm; Fig. 6A). Ventricular ectopy decreased to 26 events per 24 hours. Although a brief episode of paroxysmal ventricular tachycardia was noted (Fig. 6B), the frequency of sinus arrests lasting greater than 6 seconds dropped substantially from 36 to 22 episodes. AVBs were observed preceding sinus pauses (Fig. 7), whereas junctional escape rhythms or supraventricular arrhythmias occurred following sinus pauses. Consequently, maintenance therapy with theophylline (8 mg/kg PO q24h) and hyoscyamine sulfate (0.004 mg/kg PO q8h) was continued unchanged.

Discussion

Sick sinus syndrome (SSS), a syndrome characterized by sinus bradycardia, sinus pause or arrest, and sinoatrial block, is often accompanied by escape rhythms. It may manifest as periods of supraventricular tachycardia alternating with bradyarrhythmia known as “bradycardia-tachycardia syndrome”. However, the pathogenesis of sick sinus syndrome in dogs is not clearly understood (Kavanagh, 2002; Burrage, 2012; Santilli et al., 2018), but histopathological depletion of nodal cells with fatty and fibrofatty changes in dogs with SSS has been reported (Machida and Hirakawa, 2021). The patient in this report was an aged female West Highland White

Terrier presented for syncopal episodes, a characteristic clinical manifestation of SSS. Initial electrocardiography revealed sinus bradycardia, while a subsequent ECG during echocardiography identified concurrent sinus pauses, strongly supporting a diagnosis of SSS. Although atropine administration elicited a positive chronotropic response (heart rate increased from 60 bpm to 140 bpm), the co-occurrence of syncope and documented sinus pauses indicated intrinsic sinoatrial node dysfunction rather than physiological vagotonia. Diagnostic confirmation was subsequently achieved via 24-hour Holter monitoring; collectively, the patient's signalment, clinical signs, baseline ECG, atropine response, and Holter findings established the diagnosis of SSS.

An atropine response test was performed using subcutaneous injection at 0.04 mg/kg, resulting in a heart rate elevation to 140 bpm in this case. In dogs presenting with sinus bradycardia, a positive atropine

response classically suggests hypervagotonia secondary to extracardiac pathologies, including gastrointestinal, respiratory, intracranial, or ocular (glaucoma) conditions, as well as endocrinopathies such as hypothyroidism (Willis *et al.*, 2018). While these disorders represent key differential diagnoses, a positive atropine challenge does not exclude intrinsic sinoatrial node disease, as many dogs with SSS retain partial or complete chronotropic responsiveness (Santilli *et al.*, 2018; Willis *et al.*, 2018). Consequently, the diagnostic utility of atropine testing in discriminating normal from diseased dogs and in predicting pharmacological response remains limited (Santilli *et al.*, 2018; Willis *et al.*, 2018). A definitive diagnosis of SSS in clinical practice must therefore rely on the combined synthesis of baseline ECG and continuous 24-hour ambulatory Holter monitoring rather than atropine responsiveness alone (Santilli *et al.*, 2018).

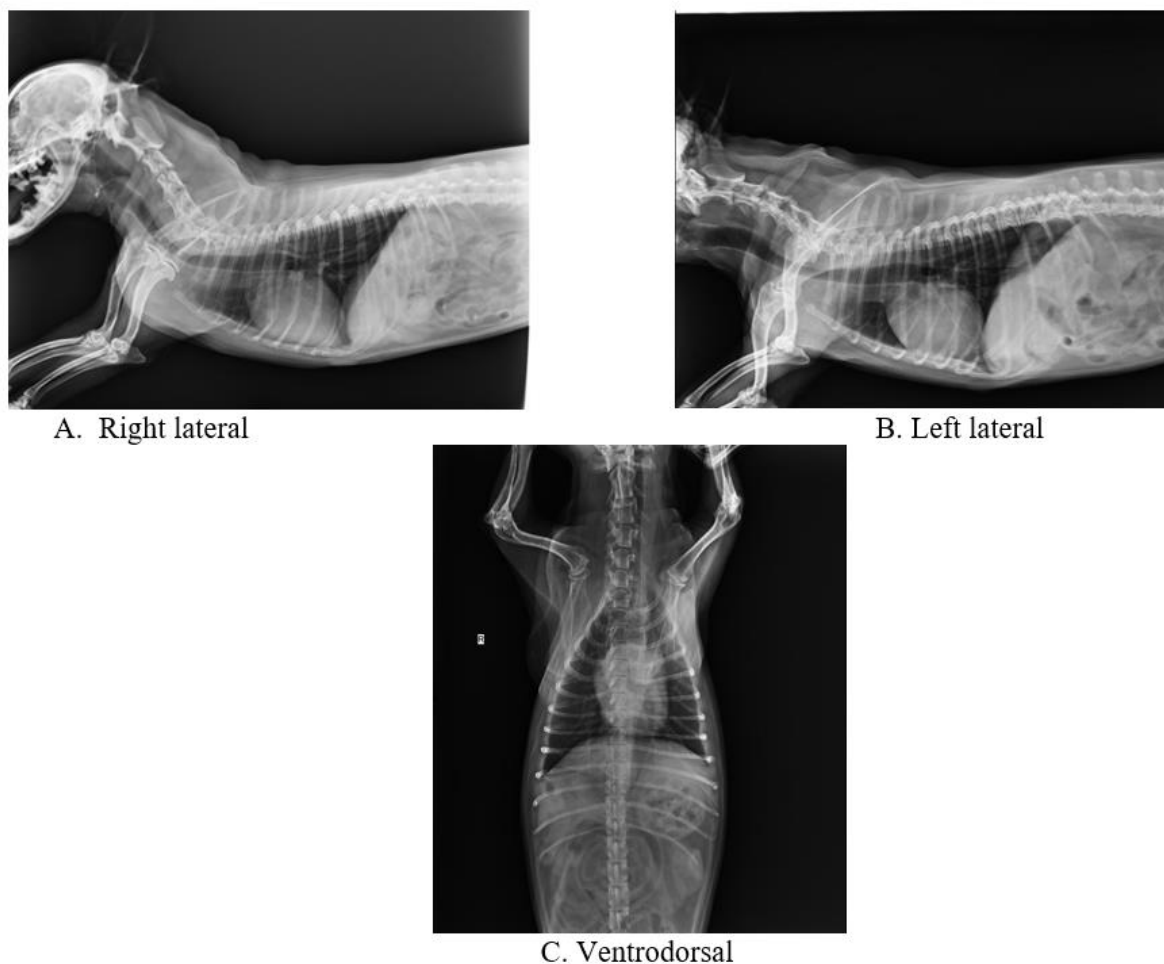


Figure 1 Thoracic radiographs (A, B and C) demonstrate a cardiac silhouette within normal size. The pulmonary vasculature is unremarkable, and the lung fields are clear without evidence of pulmonary edema, pleural effusion, or other clinically significant thoracic abnormalities.

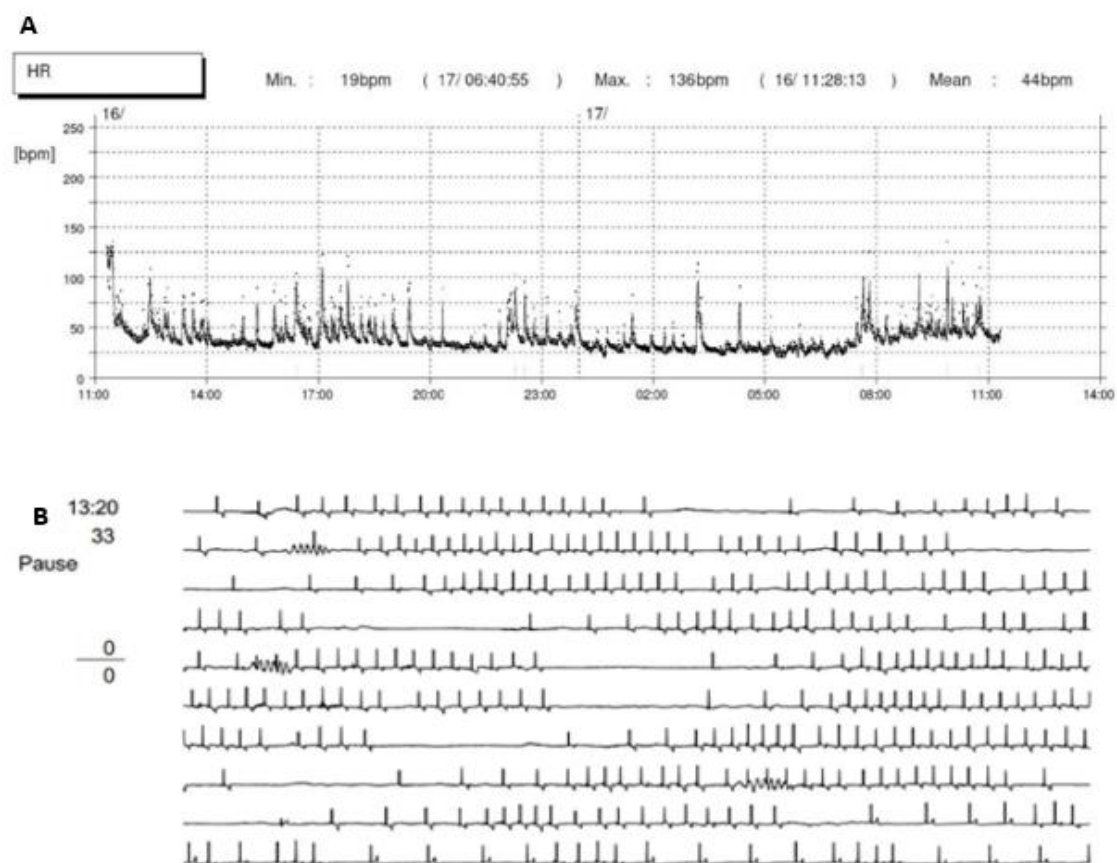


Figure 2 The first Holter monitoring (before treatment) shows bradycardia-tachycardia patterns with the minimal, maximal, and mean heart rates about 19, 136, and 44 bpm respectively (A) and multiple sinus pauses with junctional and ventricular escape beats (B).



Figure 3 The in-hospital ECG is recorded after 2 weeks of medications using hyoscyamine and theophylline. The ECGs reveal sinus rhythm (A) and supraventricular arrhythmia (B) with heart rates between 120-150 bpm.

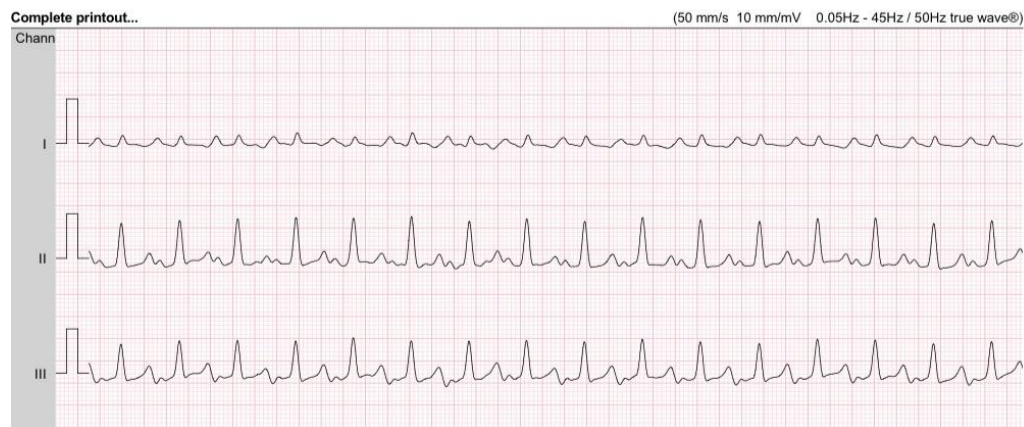


Figure 4 The hospital ECG shows a pattern of sinus tachycardia with a heart rate of 240 bpm, measured after treatment for nine months with Hyoscyamine sulfate (0.004 mg/kg PO q8h) and theophylline (8 mg/kg PO q12h).

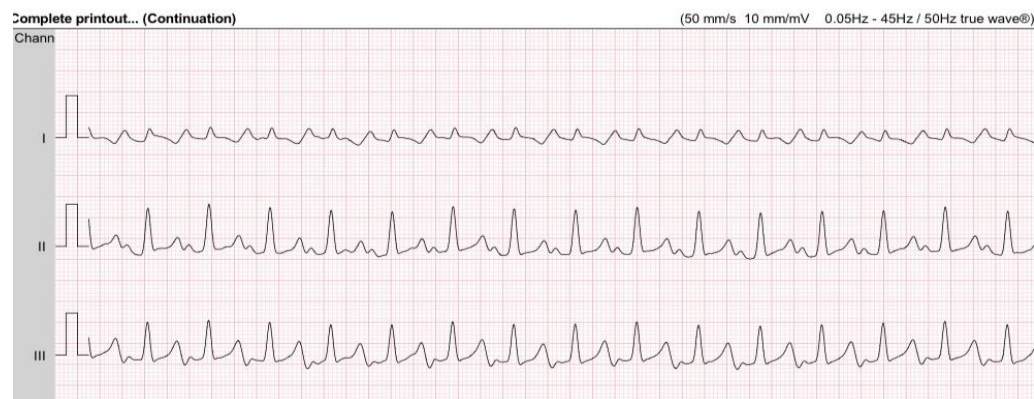


Figure 5 The hospital ECG shows a decrease of heart rate from 240 bpm (as shown in figure 4) to 220 bpm, measured after adjusting the Hyoscyamine dose from 0.004 mg/kg PO q8h to 0.004 mg/kg PO q12h and maintaining theophylline at a dose of 8 mg/kg PO q12h.

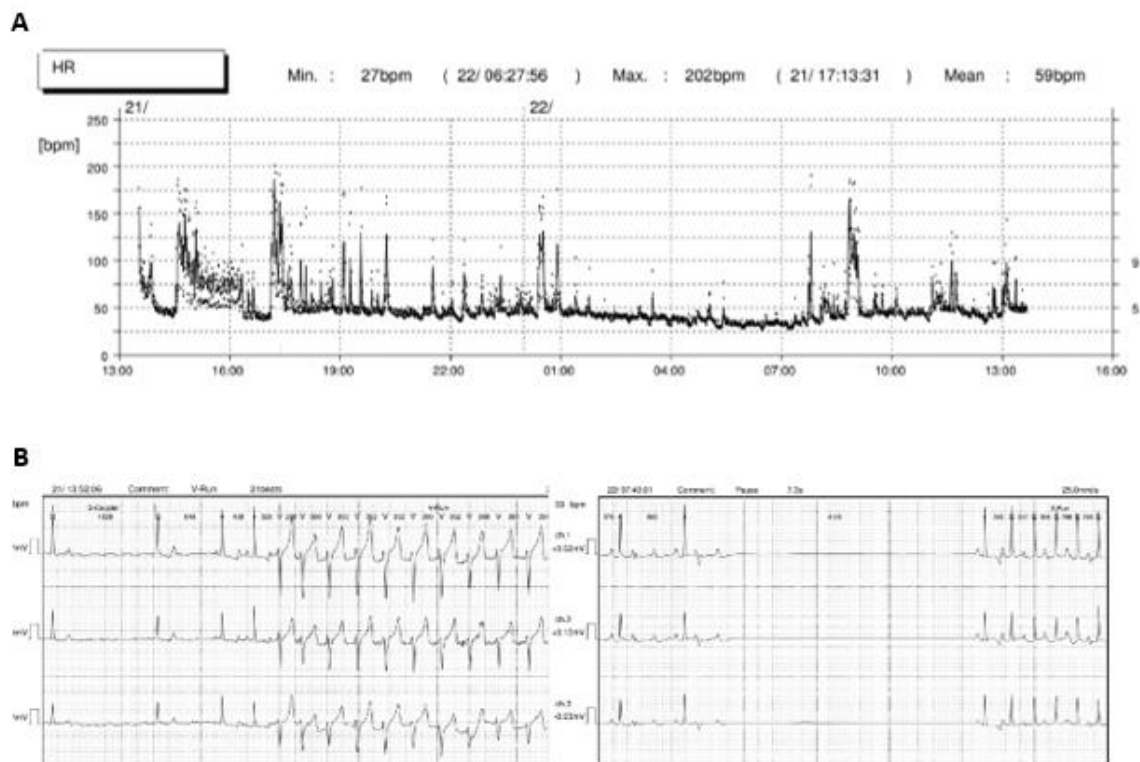


Figure 6 The minimal, maximal, and mean heart rates of 24-hour ECG are 27, 202, and 59 bpm respectively as shown in (A). The second Holter monitoring (after treatment for one year) reveals an episode of paroxysmal ventricular tachycardia (B, left) and supraventricular tachycardia (B, right) after pauses.

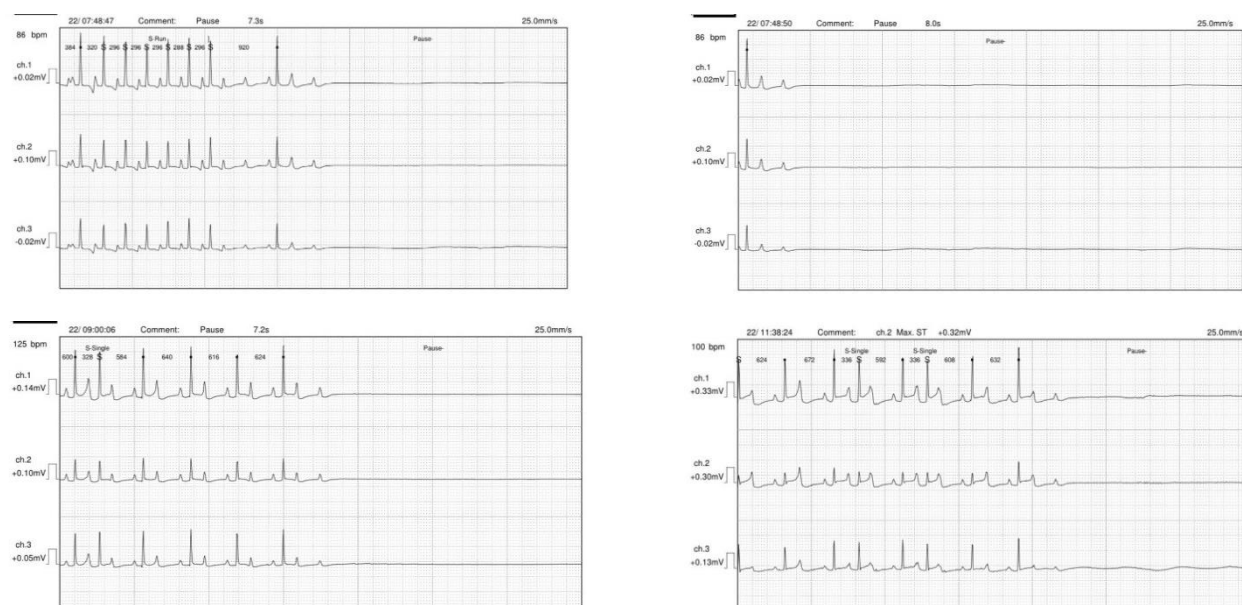


Figure 7 The ECGs reveal a pattern of atrioventricular block before sinus arrest in 4 events.

Pharmacological management of bradycardia may involve combining a vagolytic agent with either a phosphodiesterase inhibitor or a sympathomimetic drug. Following a positive response to the atropine challenge test, combination therapy with the vagolytic agent hyoscyamine sulfate and the phosphodiesterase inhibitor theophylline was initiated in accordance with established protocols (Kraus and Gelzer, 2016). Theophylline, a xanthine derivative that inhibits phosphodiesterase and increases intracellular cyclic adenosine monophosphate (cAMP) has been indicated for the management of sick sinus syndrome (Park *et al.*, 2005) and atrioventricular blocks (AVBs) in human medicine (Haught *et al.*, 1994; Bertolet *et al.*, 1995; Tai *et al.*, 2023). Additionally, hyoscyamine sulfate binds to cardiac and gastrointestinal muscarinic receptors and is frequently utilized to increase heart rate in patients with bradyarrhythmias, AVBs, or myasthenia gravis (Gehi *et al.*, 2008; Thomason *et al.*, 2019). However, concurrent administration of these agents may exert additive or synergistic pharmacological effects. Prior to intervention, the patient experienced a particularly severe syncopal event characterized by extremity rigidity and opisthotonus lasting approximately three minutes, followed by a 20-second recovery period marked by tachypnea and lethargy. Given the severity of this episode, combination therapy was initiated rather than monotherapy. Although the combination of hyoscyamine and theophylline effectively alleviated clinical signs by increasing heart rate, both agents carry risks of dose-dependent adverse effects (Thomason *et al.*, 2019). As an anticholinergic agent, hyoscyamine sulfate may induce tachycardia, mydriasis, mucosal dryness, gastrointestinal dysmotility, and urinary retention; conversely, theophylline may cause gastrointestinal distress, muscular tremors, tachycardia, and hyperexcitability. Consequently, meticulous dose titration and close monitoring are required to optimize therapeutic benefit while limiting adverse effects, with dosage adjustments or treatment cessation indicated upon signs of significant toxicity.

Ventricular arrhythmias were evaluated and categorized using a modified Lown-Wolf grading system: grade 0, absent; grade 1, isolated VPCs; grade 2, ventricular bigeminy or trigeminy; grade 3, accelerated idioventricular rhythm; grade 4, ventricular couplets or triplets; and grade 5, ventricular tachycardia (Romito *et al.*, 2026). In cases presenting with multiple arrhythmia types, classification was assigned based on the highest degree of arrhythmic complexity. On the first Holter monitoring, the patient's ventricular arrhythmia was classified as grade 4 due to the presence of ventricular couplets (Romito *et al.*, 2026). However, antiarrhythmic drugs for ventricular arrhythmias were not prescribed because most of them exert the negative chronotropic effect that could exacerbate the underlying bradycardia and counteract the primary treatment.

In summary, a combination of hyoscyamine sulfate and theophylline can be considered as an alternative treatment of dogs with SSS but tachyarrhythmias may be considered as an additional adverse effect. Drug dosage adjustment and continuous ambulatory ECG monitoring are necessary for a successful outcome. Continuous ambulatory ECG monitoring during diagnosis and initial therapy is equally vital for a successful outcome.

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