# Transient Atrioventricular Block Associated with Acute Pancreatitis in a Japanese Chin Dog

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## ABSTRACT

Electrocardiographic changes (ECG) are a common complication of acute pancreatitis (AP), although their etiology and pathogenesis remain unclear. Commonly reported electrocardiographic changes in human beings with AP include non-specific changes of the ventricular repolarisation process, and various kinds of conduction and/or rhythm anomalies. The association between AP and ECG abnormalities has not been investigated in the veterinary literature. We report a case of a previously healthy Japanese Chin dog with acute pancreatitis demonstrating severe bradycardia, ST-segment depression, atrial standstill, 2$^{nd}$ and then 3$^{rd}$ degree atrioventricular block, all of which were resolved once the pancreatitis ameliorated. We conclude that due to the transient nature of such ECG findings in patients with AP, as long as haemodynamics remain or can be maintained stable, decisions regarding permanent pacemaker therapy or euthanasia should be made with caution.

**Keywords:** Atrial standstill; Atrioventricular block; Bradycardia; Canine; ECG; Pancreatitis.

## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas associated with local and systemic manifestations (1). The clinical course of pancreatitis varies between patients from mild clinical signs such as vomiting and abdominal discomfort to severe fulminating sequels such as systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (1, 2). Systemic complications of AP include acute kidney injury (AKI), coagulopathy, acute respiratory distress syndrome and cardiac arrhythmia (1).

Tachyarrhythmia (such as supraventricular premature complexes, atrial flutter or atrial fibrillation) bradyarrhythmia, and bundle branch block, have all been associated with AP in human beings (2). Although veterinary textbooks mention arrhythmia as a potential sequel of pancreatitis (1), to the best of the authors' knowledge the veterinary literature lacks clinical case reports that describe this phenomenon.

The present report describes the clinical course of a 7 year old intact female Japanese Chin dog with AP, complicated by AKI and multiple electrocardiographic (ECG) changes, including bradyarrhythmia, ST-segment depression, atrial standstill, and atrio-ventricular (AV) block, all of which resolved once pancreatitis ameliorated.

## CASE SUMMARY

A 7 year old intact female Japanese Chin dog was referred to a Koret School of Veterinary Medicine university teaching hospital emergency department with chief complaints of vomiting, anorexia, weakness and depression of 3 days duration. The dog was treated by the referring veterinarian

with intravenous (IV) fluids and broad-spectrum antibiotics, with no significant improvement over the following two days.

Physical examination at presentation revealed hypothermia with a rectal temperature of 36.4˚C, a normal respiratory rate of 20 breaths/minute, normal mucous membrane color with a prompt capillary refill time, and a normal heart rate (HR) of 100 beats/minute) (BPM) with an auscultated arrhythmia. The dog was in good body condition (BCS=4 / 9, body weight = 5.2 kg), estimated to be 6% dehydrated, not ambulatory and depressed. Pain and discomfort were noted upon cranial abdominal palpation.

A complete blood count (CBC) showed mild leukocytosis (22.0 x $10^3$ /µL, Reference interval (RI): 8.0-17.0), with a mild mature neutrophilia (19.0 x $10^3$ /µL, RI: 3.6-13.1) and hemoconcentration (Hematocrit 60.8%, RI: 37.0-55.0; RBC 9.4 x $10^6$ /µL, RI: 5.0-8.1). No toxic changes of the neutrophils were noted on a direct blood smear microscopic examination.

A complete serum biochemical panel taken by the referring veterinarian a day before admission revealed elevations in albumin and total protein (4.7 g/dl, RI: 2.3-4.5, and 8.5 g/dl, RI: 4.9-7.2, respectively), elevated alanine transaminase (ALT, 124 U/L, RI: 6-70), aspartate transaminase (AST, 65 U/L, RI: 10-43), creatinine (2.3 mg/dl, RI: 0.5-1.5) and urea (201.7 mg/dL, RI 10-60). Electrolyte abnormalities included hypocalcemia (7.9 mg/dL, RI: 9.1-11.7), hyperkalemia (6.6 mmol/L, RI: 3.5-5.4) and hyperphosphatemia (10.6 mg/dL, RI: 2.3-6.4). Sodium and chloride levels were normal (149 mmol/L, RI: 139-150 and 102 mmol/L, RI: 97-120, respectively). Sodium to potassium (Na : K) ratio was low at 22.

On presentation, creatinine was further elevated at 2.5 mg/dl and the hyperkalemia began to resolve with a potassium of 5.5 mmol/L. Sodium and chloride concentrations decreased (133 and 96 mmol/L, respectively). Urinalysis showed isosthenuria with hyaline and granular casts, indicating renal tubular damage, attributed to AKI. Based on the low Na:K ratio an ACTH stimulation test was performed to rule out hypoadrenocorticisim (Base cortisol - 11.6 µg/dL, RR:1.3-7.2).

Abdominal ultrasound revealed a corrugated and thickened duodenal wall and a hypo-echoic pancreas, both of which were strongly suggestive of AP. No chronic structural changes were demonstrated in the kidneys and there was no evidence of free abdominal fluid. The ultrasonographic findings, combined with the clinical history, physical examination and blood work abnormalities, were indicative of primary AP, with AKI suspected to be a secondary complication.

The dog was treated with an IV bolus of 20 ml/kg Lactate Ringers Solution (LRS) (Teva Medical, Ashdod, Israel), followed by 5ml/kg/hr, metoclopramide (Pramin, Rafa laboratories, Jerusalem, Israel, 1mg/kg/day, for 4 days), an H2 blocker (Famotidine, West-Ward, United states, New Jersey, 1 mg/kg, IV, q24h), ampicillin (Penibrin, Sandoz, Pyrmont, Australia, 20mg/kg, IV, q12h) and buprenorphine (Siegfried, Switzerland) 0.01 mg/kg, IV, q6h). Due to its low body temperature the patient was warmed with a blower. Vital signs, semi-quantitative urine output, body weight, indirect blood pressure and ECG were all monitored.

Eight hours after admission, breathing rate increased to 60 breath/minute along with a decreased HR of 35-40 BPM. A Lead-II ECG rhythm strip performed over 120 consecutive seconds in right lateral recumbency at 25 mm/s and 10mm/mV, with no filtering (Nihon Kohden, Cardiofax GEMECG-9029K, Japan), revealed a slow, irregular rhythm lacking P waves, with ST-segment depression (0.3 millivolts) as well as T-wave inversion (discordant to the dominant R-wave of the QRS complex) (Figure 1). These findings were compatible with atrial standstill along with a junctional escape rhythm. However, as many of the pauses were recorded

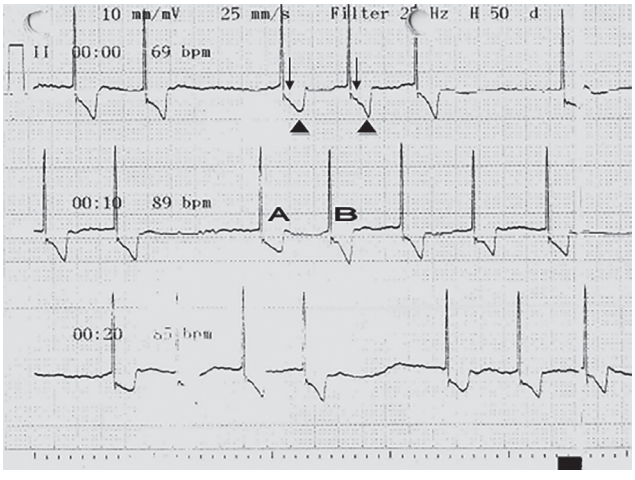


**Figure 1:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 1. Note the irregular heart rhythm with a heart rate of 72 BPM, the absence of P waves, an ST-segment depression (0.3 millivolts) (black arrows), and T-waves (arrowheads) of two separate amplitudes (labeled A and B).

to be as long as an exact multiplication (x2) of the R-to-R interval, a sino-atrial block could not be ruled out.

Furosemide (Fusid, Alfasan, Woerden, The Netherlands, 2 mg/kg, IV, once) was empirically administrated to relieve pulmonary edema, suspected based on the documented tachypnea, and oxygen was administered via a mask. Immediately following atropine sulphate administration (Atropine, Teva pharmaceuticals, Israel, Petach Tikva, 0.02 mg/kg, IV, once) a repeated ECG rhythm strip showed occasional re-initiation of P waves followed by QRS complexes with a persistent PR interval. However, the only occassional repetitive PR-interval may have been incidental and these complexes were nonconsecutive and were therefore not necessarily consistent with capture beats. Also, in this strip, some of the T waves were deeper than others in peak amplitude, potentially suggestive of more than a single escape focus (Figure 2).

Over the next day the dog improved clinically, vomiting ceased and body temperature and breathing rate normalized. Repeat creatinine, potassium, sodium and ionic calcium all measured within normal RI's. Electrocardiography, however, demonstrated the same pattern of bradycardia and ST-segment depression with occasional non-conducted P waves. In this strip (Figure 3), couplets with a fixed coupling interval appeared with the second complex demonstrating a deeper T-wave peak, similarly suggestive of two separate foci. Within each pair, the second complex appeared to be an "echo beat" compatible with re-entry as the underlying electrophysiological mechanism (3). Three of these couplets involved a constant PR interval, which may attest to a fusion process, where two separate depolarization fronts propagated simultaneously from two (a ventricular and a sino-atrial) foci, and collided to generate a "merged" QRS complex morphology (Figure 3).

At this point treatment with atropine (0.02mg/kg IV q6h) was restarted. On the next day (day 3), the dog had regained its appetite. It was still bradycardic at 30 BPM, and a 3rd degree atrioventricular block with ventricular escape beats of the deeper T-wave amplitude were recorded (Figure 4).

On day 4, HR was 33 BPM. Electrocardiography revealed a low grade, 2nd degree, Mobitz Type II, atrioventricular block (Figure 5) with ventricular escape beats of the deeper-T wave morphology. To increase the sympathetic tone, beta adrenergic agonists, terbutaline (Terbutaline sulphate, Vitamed, Binyamina, Israel, 0.2 mg/kg, PO, q8hr), and isoproterenol (Isoprenalina cloridato, Monico spa, Italy, Venezia, 0.4 mg in 250 mL d5W, SIV), and theophylline, a phosphodiesterase inhibitor (Theotrim, Trima, Kibbutz Maabarot, Israel, 6 mg/kg, PO, q12h) were added to the treatment regimen. Twelve hours later the dog had a grand mal seizure which was controlled by an IV bolus of diazepam (Assival, Teva pharmaceuticals, Petach Tikva, Israel, 2.5 mg, IV). Treatment

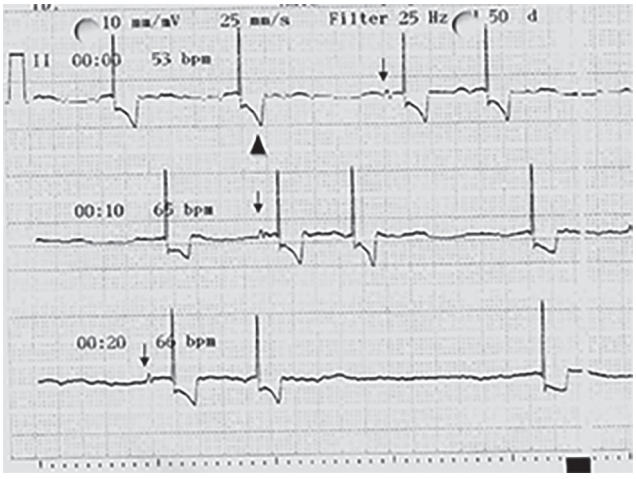


**Figure 2:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 1, following intravenous administration of atropine (0.02 mg/kg). Note the occasional re-initiation of P waves followed by QRS complexes with only occassional repeated PR interval (black arrows) and deepening of some of the T waves (arrowheads), compatible with the morphology labeled B in Figure 1 (see text for details).

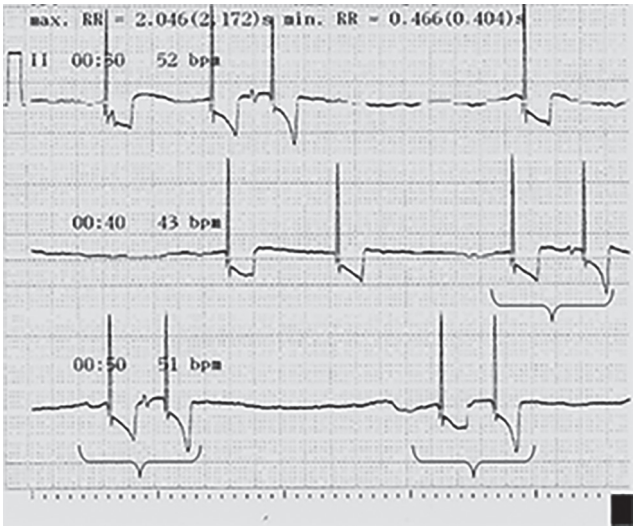


**Figure 3:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 2. Note the initiations of couplets with a fixed coupling interval (three of which are underlined by horizontal brackets). The second complex in each such couple demonstrates a relatively deeper T-wave peak, compatible with the morphology labeled B in Figure 1 (see text for details).

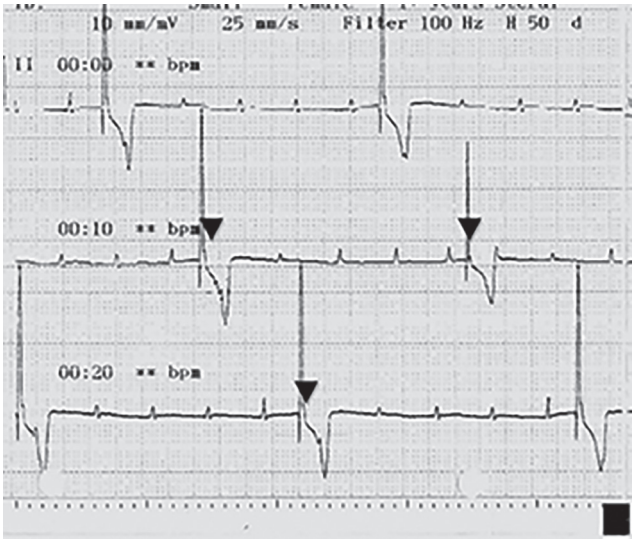


**Figure 4:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 3, following intravenous atropine (0.02 mg/kg) administration. Note the isolated, generally evenly-spaced P-waves (often superimposed on the descending limb, peak, or offset of the T-wave) with no constant PR-interval, consistent with a 3rd degree atrioventricular block with escape beats (arrowheads).

with isoproterenol and theophylline was discontinued and the dog was discharged with only oral terbutaline for 3 more days.

Upon follow-up examination on day 7, the owner reported that the dog has made a complete recovery. Pulse rate had increased to 80 BPM and an ECG rhythm strip revealed normal sinus arrhythmia, with a single non-conducted P-wave and no ST-segment depression (Figure 6). Unfortunately, repeated ultrasound or blood-work was not allowed. A repeated ECG a month later was similarly normal.

## DISCUSSION

Pancreatitis is an inflammation of the pancreas which is commonly associated with severe systemic complications (1). The exact prevalence in dogs is unknown but the condition is considered relatively common (1). Although several etiologies have been suggested, including dietary changes, a fat-rich diet, obesity, use of drugs such as potassium bromide, L-asparginase, tetracycline and azathioprine, surgical manipulation, or blunt abdominal trauma and shock, in most cases the etiology remains unknown (1, 4).

Acute pancreatitis develops as a result of premature activation of zymogens, which leads to auto-digestion, resulting in stimulation of an inflammatory reaction. Most dogs with AP present with weakness, vomiting, depression, abdominal pain and diarrhea (5). Systemic manifestation such as shock, dehydration, jaundice, respiratory distress, bleeding disorders and cardiac arrhythmia are also seen in the more severe cases (1).

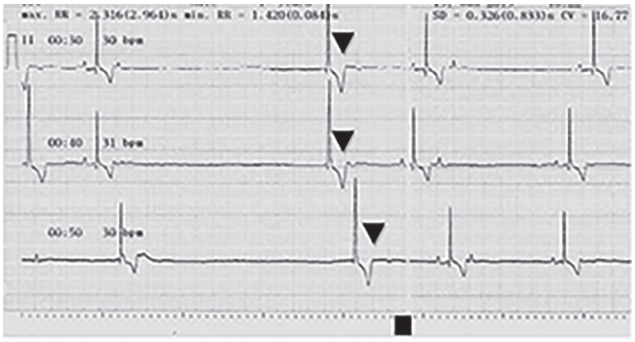


**Figure 5:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 4. Sinus beats are presented with ventricular escape beats of the deeper-T wave type (arrowheads) following longer pauses, compatible with the diagnosis of a 2nd degree, Mobitz Type II, atrioventricular block (see text for details).

Diagnosis of AP in dogs is challenging due to a low sensitivity and specificity of the available diagnostic tests (1,

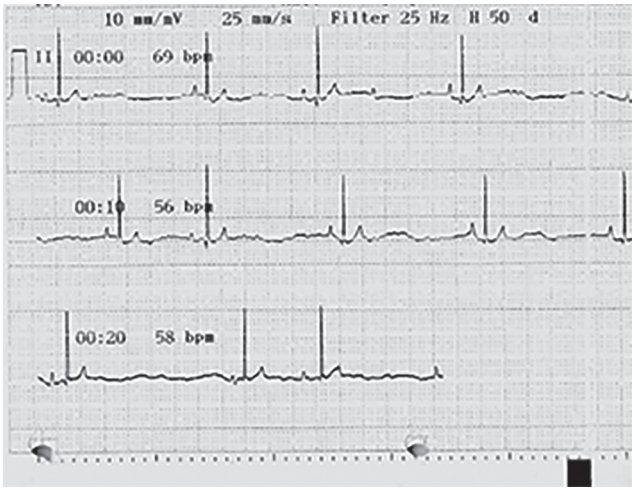


**Figure 6:** An ECG rhythm strip (Lead II, 25 mm/sec, 10 mm/mV.) of a 7-year-old female Japanese Chin dog presented for AP, recorded on day 7. Normal sinus arrhythmia is present, (including transient, second degree atrio-ventricular block, recorded following the third complex) with a normal heart rate, and normal amplitudes and intervals (see text for details).

6). Therefore, signalment, clinical signs, blood work, as well as imaging diagnostics should all be taken into account (6). The gold standard is considered histopathology. However, acquiring a pancreatic biopsy requires an invasive procedure. In addition determining the clinical significance of histopathological findings is considered challenging: there are no standardized criteria that distinguish microscopic findings leading to clinical disease from those that do not. On the other hand, inflammatory lesions of the pancreas are often localized and can easily be missed (6). Abdominal ultrasonography, a non-invasive procedure, is considered relatively sensitive (70%) and highly specific when performed by an imaging specialist (1, 6, 7), as was done in this reported case.

Pancreas specific blood tests including pancreas-specific lipase (cPLI), and serum amylase and lipase levels, all have relatively low sensitivities (1, 7). Among these, cPLI is considered to have the highest sensitivity and specificity (78% and 81% respectively). Unfortunately, in the reported case, due to financial constraints, no specific blood tests were undertaken.

Pre-renal azotemia is often seen due to dehydration or shock, or due to direct renal damage resulting in AKI (1) secondary to hypovolemia, ischemia, or intravascular coagulopathy, or due to peritonitis secondary to the local inflammatory process resulting from the pancreatic proteolytic activity (8). In the present case the combination of an elevated serum creatinine level, minimal dehydration upon admission, normal kidney structure in abdominal ultrasonography, and urinary hyaline and granular casts, indicated the presence of AKI. It is important to note that AKI can also cause metabolic changes such as metabolic acidosis and elevated potassium levels that can influence cardiac activity and electrophysiology, however in the reported case AKI resolved within 24 hours of treatment and cardiac arrhythmias persisted for the next few days.

Cardiovascular effects associated with human AP include cardiac rhythm abnormalities, decreased ventricular contractility, and changes in the vasomotor tone of peripheral vessels (2, 9, 10). The reported occurrence of ECG abnormalities in human AP patients is as high as 55% (10). Tachyarrhythmia such as supraventricular premature complexes, atrial flutter or atrial fibrillation, bradyarrhythmia, and bundle branch block, have all been reported in human patients with AP (2). However, in only 3.9% of the patients more than one of such abnormalities was documented upon admission (10). The dog reported here demonstrated several ECG abnormalities (e.g. ST-segment depression, AV block, atrial standstill) in the course of its 4 day long hospitalization period, none of which was a tachyarrhythmia. Acute pancreatitis in human beings is commonly associated with nonspecific changes of repolarization, mainly T-wave inversion and ST-segment depression or elevation (11, 12). In the present case there was an ST-segment depression of 0.3 mV, possibly caused by transient myocardial hypoxia, or by hyperkalemia (12).

The pathogenesis and clinical relevance of ECG abnormalities observed in patients with AP are unclear (2, 10). Several mechanisms have been proposed, including a direct toxic effect of the pancreatic proteolytic enzymes on the heart causing myocardial infarction (11), pancreatitis induced coagulopathy, increased platelet adhesiveness (13), and electrolyte disturbances (2, 9, 10), all of which are common complications of AP. A high occurrence of metabolic disturbances, including electrolyte imbalances, is also reported in veterinary patients with AP (1). In a study describing the occurrence of cardiac arrhythmia in human AP patients there was no correlation between pancreatic enzyme levels (lipase, amylase and pancreatic amylase) and ECG abnormalities. However, there was a correlation between ECG abnormalities and phosphorus, calcium and potassium imbalances (10). These results, combined with the rapid onset of ECG changes in AP patients, suggest that electrolyte imbalances, rather than direct myocardial damage due to enzymatic changes, may play a major role in the pathogenesis of ECG abnormalities in AP (10). Hypocalcemia and hyperkalemia were indeed existing in the presently reported case. However, ECG abnormalities continued after the resolution of these electrical imbalances, rendering them less likely to be the main contributors to the documented ECG changes.

Cardiac Tropoin (cTn), a myofibrillar protein that is released from injured myocardiocytes, is considered the gold standard biomarker to assess myocardial injury in humans regardless of the overlying etiology. It was also found effective in detecting, monitoring and quantifying ongoing cardiac injury in veterinary medicine (14). No serum samples were available to measure troponin levels retrospectively, which is a limitation of the reported case.

Regardless of the cause, in most human patients with AP there is a complete resolution of ECG abnormalities once the patient recovers from AP (2, 15-17), as was also seen in the presently reported case. Therefore, in cases of severe bradyar-

rhythmia (e.g. 3rd degree AV block, atrial standstill) associated with acute AP, permanent pacemaker implantation as well as decisions about possible euthanasia should be postponed or avoided altogether in the acute phase of the disease (as long as hemodynamic stability can be maintained), due to the typically transient nature of the bradyarrhythmia, as also seen in the present case.

The presently reported patient experienced a single seizure episode. AP can trigger seizure activity by causing severe electrolyte imbalances or by inducing brain thromboembolism. However, since the dog had clinically improved, intracranial clot embolization appeared less likely to have caused a seizure. Other possible causes include drug induced CNS excitability. Theophylline administration has been reportedly associated with seizure activity in both dogs and humans (18, 19), while terbutaline has been reported to induce tremors in dogs (20) as has isoproterenol in humans (21).

In summary, although AP has been widely associated with ECG abnormalities in human beings, specific anomalies have not yet been reported in the veterinary literature. In the present case, a previously healthy dog with AP demonstrated severe bradyarrhythmia and ST-segment depression, all of which proved to be transient. As the development of severe bradyarrhythmia such as a 3rd degree AV-block can sometimes lead to euthanasia, it is important that veterinarians be aware of the possible transient nature of such bradyarrhythmia in patients with acute pancreatitis. Further prospective and larger scale studies are indicated to establish whether ECG abnormalities are in correlation with clinical signs, healing time, systemic complications, and prognosis, as well as to better assess the required treatment and its effect on ECG changes in pets with AP.

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