

BRADYARRHYTHMIAS IN DOGS WITH EXOCRINE PANCREATIC INSUFFICIENCY

BRADIARRITMIAS EM CÃES COM INSUFICIÊNCIA PANCREÁTICA EXÓCRINA

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SUMMARY

The exocrine pancreatic insufficiency (EPI) is a digestive disease caused by atrophy or inflammation of pancreatic acinar cells, resulting in nutrient malabsorption and clinical signs related to malnutrition. Three German Shepherds were presented at the Veterinary Hospital with background and clinical signs compatible with EPI, what was confirmed by routine laboratory testing. On physical examination, both presented bradyarrhythmias confirmed by computerized electrocardiogram. After therapy for EPI, the bradyarrhythmias were solved. The authors discuss the influence of the gastrointestinal hormone cholecystokinin, which can increase in pancreatic exocrine impairment, possibly reflecting a failure to provide feedback down-modulation of CCK release, causing cardiovascular effects, such as chronotropic and inotropic negative actions and promoting bradycardia.

KEY-WORDS: Arrhythmia. Electrocardiography. Cholecystokinin. Gastrointestinal

RESUMO

A insuficiência pancreática exócrina (IPE) é uma enfermidade causada por atrofia ou inflamação das células acinares pancreáticas, resultando em má absorção de nutrientes e sinais clínicos relacionados à desnutrição. Três pastores alemães foram atendidos no Hospital Veterinário com histórico e sinais clínicos compatíveis com IPE, diagnosticada através de testes laboratoriais de rotina. Ao exame físico, os três animais apresentaram bradiarritmias, que foram confirmadas por eletrocardiograma computadorizado. Após o tratamento da IPE, houve normalização dos valores de frequência cardíaca de todos os pacientes. Os autores discutem a influência do hormônio colecistoquinina, que pode estar elevado em casos de insuficiência pancreática exócrina e que, por sua vez, exerce efeitos cardiovasculares tais como cronotropismo e inotropismo negativos, promovendo desta forma a bradicardia destes pacientes.

PALAVRAS-CHAVE: Arritmia. Eletrocardiografia. Colecistoquinina. Gastrointestinal

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INTRODUCTION

The most common causes of exocrine pancreatic insufficiency in dogs are chronic pancreatitis and pancreatic acinar atrophy, which occur most commonly in German Shepherds and which have been shown to be hereditary in this breed. The exocrine pancreas has an exceptional reservation and the clinical signs only develop when more than 90% of the acinar cells are lost. Depending on the duration of the disease, voluminous soft stools, increased frequency of defecation, severe weight loss and ravenous appetite, malnutrition, poor haircoat and other dermatologic signs are the most common complaints from owners. In most affected dogs, enzyme deficiency is complicated due to concurrent small intestinal bacterial overgrowth, which probably contributes to cobalamin malabsorption often leading to subnormal serum concentrations of this vitamin (WILLIAMS, 1997, RUTZ et al., 2001).

Cholecystokinin (CCK) is a gastrointestinal hormone released from enteroendocrine cells lining the intestinal mucosa in response to feeding (SARTOR & VERBERNE, 2008). Receptors found in the duodenum detect fat, free fat acids, amino acids and proteins present on chyle, and induce the release of cholecystokinin (CCK). The cholecystokinin has many physiological actions, including the classic effects on pancreatic enzyme secretion and gallbladder contraction, stimulation of intestinal and colonic motility and increase of gastric emptying (OTSUKI, 2000).

Marker and Roberts (1988) and Fossa et al. (1997) described negative chronotropic actions of cholecystokinin on the rat heart. The receptors in rat heart were similar to the classes of cholecystokinin receptors found in exocrine pancreas. In addition, Zhao et al. (2002) reported that high-to-medium doses of cholecystokinin caused bradycardia and increased left-ventricular systolic pressure. The CCK-evoked bradycardia occurs via a direct action at cardiac CCK receptors (SARTOR & VERBERNE, 2002).

The CCK-8 also has an inotropic effect and induces bradycardia in rats regardless the stimulation or blockade of beta-adrenoceptors (WISNIEWSKA & WISNIEWSKI, 1996). A dose of CCK-4 that caused a robust and reproducible increase in mean arterial blood pressure and decrease in heart rate in dogs was determined to range from 1 to 20 µg/kg, administered intravenously in bolus. The cholecystokinin effects on the heart rate appear to be dose-dependent and to change with the species (SARTOR & VERBERNE, 2008).

Thus, the goal of the present report is to notify the occurrence of bradyarrhythmias in three dogs with exocrine pancreatic insufficiency and discuss the possible etiology and evolution after initiation of therapy for exocrine pancreatic insufficiency.

MATERIALS AND METHODS

Three German Shepherds with severe malnutrition, cachexia, poor haircoat, and background of polyphagia,

weight loss, soft feces and steatorrhea were brought to the Veterinary Teaching Hospital of São Paulo State University (UNESP), Campus of Jaboticabal, Brazil, for consultation. At the clinical examination, the animals presented alterations compatible with malnutrition, besides bradycardia on cardiac auscultation.

In the first case, a 1y2m-old female dog presented 60 beats/minute on cardiac auscultation. In another case, a 1y6m-old male dog, the heart rate was 40 beats/minute at initial clinical examination. Finally, a 2y6m-old female dog presented 54 beats/minute on cardiac auscultation. In all three cases, computerized electrocardiogram² and laboratorial exams were requested (complete blood count; measurements of serum alanine-aminotransferase, alkaline phosphatase, creatinine, amylase, sodium, potassium, triglycerides, cholesterol; blood glucose; fecal cytology and quantitative analysis of fecal trypsin).

RESULTS AND DISCUSSION

Although no significant laboratorial findings were present, the absence of trypsin in three cases, in conjunction with background and clinical findings, as well as clinical improvement after therapy, supported the diagnosis of exocrine pancreatic insufficiency. The electrocardiogram of the first case revealed sinus bradycardia (heart rate of 60 beats/min) and first-degree atrioventricular block (P-R interval off 150 ms) (Figure 1). Similar findings were seen in the third case, with sinus bradycardia (heart rate of 54 beats/min) and first-degree atrioventricular block (P-R interval off 210ms) (Figure 2).

The electrocardiogram of the second case showed sinus bradycardia (heart rate of 40 beats/min) and intermittent right bundle branch block (Figure 3).

Each patient received antibiotics for seven days (metronidazole 15 mg/kg, PO, bid) to control a concurrent small intestinal bacterial overgrowth, low-fat diet containing highly digestible protein, carbohydrate sources and fibers. Dogs were also supplemented orally with pancreatic enzyme powder (15 grams with the meals).

The three dogs were examined 14 days after the therapy and both presented a normal heart rate, although the conduction disturbances of right bundle branch block and first-degree atrioventricular block remained unchanged.

These patients presented bradyarrhythmias associated to clinical aspects of exocrine pancreatic insufficiency and after therapy, the heart rate returned to normal values. Reports describing the association of cardiac changes in dogs with exocrine pancreatic insufficiency are scarce. However, a hypothesis that could explain the abnormalities shown in this report may be related to the influence of high levels of cholecystokinin during exocrine pancreatic insufficiency (SLAFF, 1985, FRIESS, 1996, OTSUKI, 2000).

¹ Computerized ECG (ECG -PC Windows XP version) - Brazilian Electronic Technology, São Paulo, SP, Brazil.

The negative feedback that limits the release of cholecystokinin occurs through the presence of fat and proteins in the intestine while they are digested and absorbed. A specific inhibition of the release of cholecystokinin also occurs by duodenal trypsin (OTSUKI, 2000). Besides being deficient in absorbing fat and proteins, dogs with exocrine pancreatic insufficiency have low concentrations of duodenal trypsin (WILLIAMS, 1997, RUTZ et al., 2001), which will block the negative feedback, increasing the stimulus to production and release of cholecystokinin. Therefore, it is likely that the dogs of this report had high levels of cholecystokinin prior to therapy. Because high cholecystokinin concentrations can lead to bradycardia through a negative chronotropic effect or reduction of the sympathetic tonus (MARKER e ROBERTS, 1988, WISNIEWSKA, 1996, FOSSA et al., 1997, ZHAO et al., 2002), the elevation of plasma cholecystokinin in these dogs might have played a role in the bradycardia observed in the presentation.

After the supplementation with pancreatic enzymes, the heart rate had returned to normal values probably due to the presence of cholecystokinin inhibition factors during the intestinal absorption of fats and proteins, and the presence of duodenal fecal trypsin (SARTOR & VERBERNE, 2002).

The importance of the CCK-induced sympathetic reflex has not been evaluated in the clinical setting yet. It is possible that this reflex has a permissive role in the cardiovascular events that occur postprandially, and may be an important contributor to the deleterious consequences of postprandial hypotensive episodes that occur in susceptible individuals (SARTOR & VERBERNE, 2002).

CCK elicits bradycardia, but this effect is probably not reflex-mediated. That highlights a major distinction between the reflex cardiovascular effects of abdominal vagal and cardiopulmonary vagal afferent activation. That suggests that the bradycardic effect was mediated by CCK-A receptors, but not by the activation of vagal afferent or efferent discharge (SARTOR & VERBERNE, 2002). Bradycardic actions of CCK have been described in the pithed rat (GAW et al., 1995) and also in the isolated perfused rat heart (MARKER & ROBERTS, 1988).

Although Bozkurt et al. (1988) demonstrated that basal and postprandial CCK levels in patients with pancreatic insufficiency do not differ from controls, other studies showed an increase in CCK levels associated with exocrine pancreatic insufficiency (SLAFF et al., 1985, FRIESS et al., 1996, OTSUKI, 2000). Slaff et al. and Friess et al. (1996) observed that pancreatic exocrine impairment is associated with elevated basal CCK levels, measured by plasmatic immunoreactivity, which may reflect a failure to provide feedback down-modulation of CCK release.

For the measurement of CCK plasma concentration, a highly specific antibody against human CCK was available. The postprandial increase in cholecystokinin secretion may be caused by the reduced secretion of pancreatic enzymes in the duodenum, via a reduced negative feedback regulation (FRIES et al., 1996).

The present report describes three dogs with exocrine pancreatic insufficiency, a gastrointestinal disease that can lead to alterations in heart rate, like bradycardia. Whether bradyarrhythmias occur in association to pancreatic exocrine insufficiency still needs to be better investigated. Therefore, dogs with exocrine pancreatic insufficiency with high cholecystokinin levels are prone to develop cardiac alterations, especially bradycardia, and the resolution can occur after the therapy. Although the measure of cholecystokinin was not performed, it is important to consider the influence and measurement of this hormone in dogs with exocrine pancreatic insufficiency.

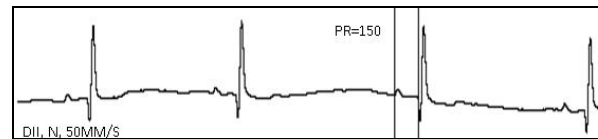


Figure 1 - The electrocardiogram of the first case, in DII derivation, sensibility N, velocity 50 mm/s, illustrating sinus bradycardia (heart rate of 60 beats/min) and first-degree atrioventricular block (P-R interval of 150 ms).



Figure 2 - The electrocardiogram of the third case, in DII derivation, sensibility N, velocity 50 mm/s, illustrating sinus bradycardia (heart rate of 54 beats/min) and first-degree atrioventricular block (P-R interval of 210 ms).

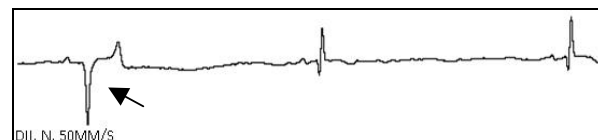


Figure 3 - The electrocardiogram of the second case, in DII derivation, sensibility N, velocity 50 mm/s, illustrating sinus bradycardia (heart rate of 40 beats/min) and nd intermittent right bundle branch block.

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