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Atrial standstill in a donkey with digitoxin intoxication

Antonia Ertelt[1], Christof A. Bertram[2], Friederike Stumpff[3], Selina Kuban[1], Robert Klopfleisch[2], Dr. Antina Lübke-Becker[4] and Heidrun Gehlen[1]

[1] Klinik für Pferde, allgemeine Radiologie und Chirurgie, Freie Universität Berlin, Berlin, Germany
[2] Institut für Tierpathologie, Freie Universität Berlin, Berlin, Germany
[3] Institut für Veterinär-Physiologie, Freie Universität Berlin, Berlin, Germany
[4] Institut für Mikrobiologie und Tierseuchen, Freie Universität Berlin, Berlin, Germany

Summary: A 15-year-old donkey gelding was referred to the Equine Clinic of the Freie Universität Berlin because of acute onset of anorexia, bradycardia and multiple syncopes. The clinical examination revealed an irregular heartbeat (11–18 bpm) and syncopes. A continuous ECG revealed absence of P-waves and an irregular ventricular escape rhythm. An echocardiography revealed a pericardial effusion with reduction of left and right ventricular function. Laboratory abnormalities revealed increased troponin I, alpha hydroxybutyrate dehydrogenase and symmetric as well as asymmetric dimethylarginine. Increased concentrations of the cardiac glycoside digitoxin was evident in serum. Clinical findings were consistent with myocarditis with pericardial effusion and atrial standstill. Because of increasing severity of symptoms and grave prognosis the donkey was humanely euthanized. Histopathological examination of the cardiac atria including the sinoatrial node revealed severe, subacute, diffuse, suppurative myocarditis.

Keywords: atrial standstill, digitoxin, cardiac glycosides, myocarditis, troponin I, SDMA, ADMA, bradycardia, cardiology, donkey

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Correspondence: Dr. Antonia Ertelt, Freie Universität Berlin, Klinik für Pferde, Berlin, Oertzenweg 19b, 14193 Berlin, Germany; antonia.ertelt@fu-berlin.de

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A 15-year-old, 253 kg donkey gelding was referred to the Equine Clinic of the Freie Universität Berlin to evaluate suspected colic and acute onset of bradycardia with multiple syncopes a few hours previously. Initial treatment by the referring veterinarian consisted of 15 ml scopolamin butylbromid in combination with metamizole (buscopan compositum®). The donkey was immediately referred to the Equine Clinic.

Abnormalities identified on physical examination included severe bradycardia (11–18 beats per minute (reference range 32–44) (*Garba* et al. 2015), tachypnea (44 breaths per minute, reference 13–25) (*Garba* et al. 2015), tremor, poor pulse quality, decreased jugular refill and peripheral hypoperfusion (capillary refill time 4–5 seconds, cold extremities, ears and muzzle). Cardiac auscultation showed an irregular rhythm with a heart rate ranging between 11 to 18 bpm. A base-apex Holter ECG (Telvet 100) with four electrodes was performed.

The ECG revealed absence of P-waves, and a variable ventricular escape rhythm at a rate of 11 bpm. The S waves were negative, with positive T waves. The RR-intervals were irregular, and ST-depression was obvious (figure 2). In the beginning, the morphology of each QRS-complex had an appear-

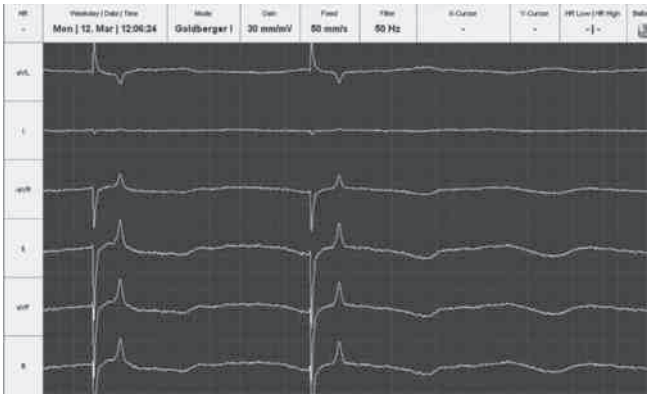

Fig. 1 A base-apex Holter ECG revealed absence of P-waves, irregular RR intervals, ST depression, positive T-waves and a variable ventricular escape rhythm at a rate of 11bpm (RR interval 5,25 s).

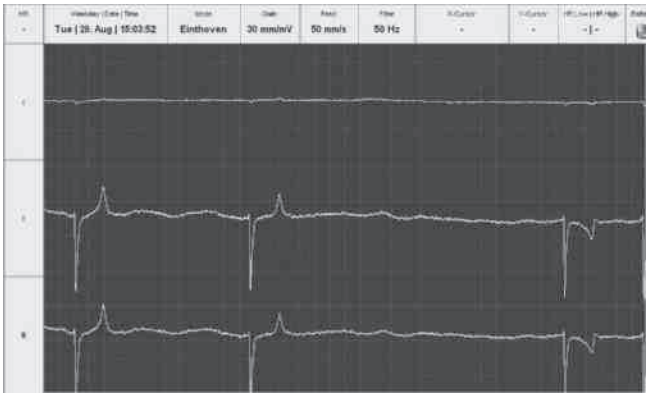

Fig. 2 QRS complexes were increased with amplitudes of 2,5 mV in lead II (reference range horse < 2.2 in lead II).

ance normal for equines (figure 1). Later, the amplitude of the QRS-complex increased to 2.5 mV in lead II (reference range horse < 2.2 in lead II) (figure 2). The donkey collapsed during ECG recording when the heart rate dropped below 13 bpm every 15 to 20 minutes. With disease progression, the T-waves became negative (figure 2), the RR-interval shortened (382 ms) and the S-wave amplitude became highly variable (1 mV–2.5 mV) (figure 3).

Echocardiographic examination (Vivid 7) revealed a pericardial effusion (figure 4). Left and right ventricular function were decreased (table 1). The atria showed no contractility. Color flow echocardiography revealed no relevant valve regurgitation.

Clinical findings were consistent with atrial standstill with a ventricular escape rhythm resulting in syncopes. Laboratory abnormalities included hemoconcentration, leukocytosis and neutrophilia (table 2). Furthermore, hyperglycemia and hyperlactatemia were obvious (table 2). The arterial blood gas analysis revealed hypercapnia and hypoxia (table 2). The donkey suffered from mixed acidosis (table 1). An increase in gamma-glutamyl transferase, blood urea nitrogen, creatinine, aspartate aminotransferase, lactate dehydrogenase and triglyceride were also present (table 2). Vitamin E (tocopherol) and selenium were within the reference range (table 2). Troponin I, alpha hydroxybutyrate dehydrogenase and symmetric as well as asymmetric dimethylarginine were increased (table 2). The catecholamine metabolites metanephrine and normetanephrine were severely increased (table 2). Despite the assertion that no glycosides had been given, assessment for digitoxin (but not for digoxin) was positive in serum (table 2).

Upon clinical admission, the donkey was suspected to suffer from severe myocarditis with pericardial effusion. Treatment with nasal oxygen insufflation, fluid administration (ringer lactate solution 80 ml/kg, hypertonic saline 7.2 % 4 mg/kg), a parasympatholytic agent (atropine 0,01 mg/kg IV), NSAID (flunixin 1.1 mg/kg IV) and broad-spectrum antibiotics (amoxicillin 10 mg/kg IV and gentamicin 2.2 mg/kg IV) was initiated. The developing tachycardia was treated with lidocaine (1.3 mg/kg bolus, CRI: 0,05 mg/kg/min). Because of increasing severity of symptoms and grave prognosis the donkey was humanely euthanized.

At a subsequent post-mortem examination, the pericardium was filled with approximately 400 ml of a clear, serous fluid. The right ventricle was mildly dilated. There were multifocal, subendocardial petechia in the ventricle and atria. Sampling of the heart for histopathology was performed as described by *Diab* et al. 2017. The recommended 11 sections of the heart were routinely sectioned and stained with hematoxylin and eosin (H&E) as well as azan for detection of collagen fibers. Histopathology of all sections including the right and left atrium (i.e. sections 1, 3–6 and 9 *Diab* et al. 2017) revealed moderate to severe, subacute, diffuse, suppurative myocarditis with pronounced hyaline degeneration of cardiomyocytes, severe intramuscular edema and severe acute hemorrhage (figure 5). Also, there were moderately increased fibroblasts and collagen fibers multifocally between the cardiomyocytes (figure 6 A and B). Inflammatory and fibrotic changes included the region around the sinoatrial node and to a lesser degree the sinoatrial node itself (section 4, figure 7) (*Diab* et al. 2017). Although the atrioventricular node was not detected by histopathology, suppurative myocarditis was also found in the region around the atrioventricular node (section 9, figure 7) (*Diab* et al. 2017). Sections of the ventricular myocardium did not reveal any changes with the exception of the occasional detection of neutrophilic granulocytes in close proximity to the valve plane.

Furthermore, there was an ascites with approximately 900 ml of a clear, serous fluid in the abdominal cavity. Histopathology of the kidneys revealed moderate dilation of the cortical tubuli and marked proximal tubular epithelial cell degeneration. Findings of the kidney are consistent with acute ischemic tu-

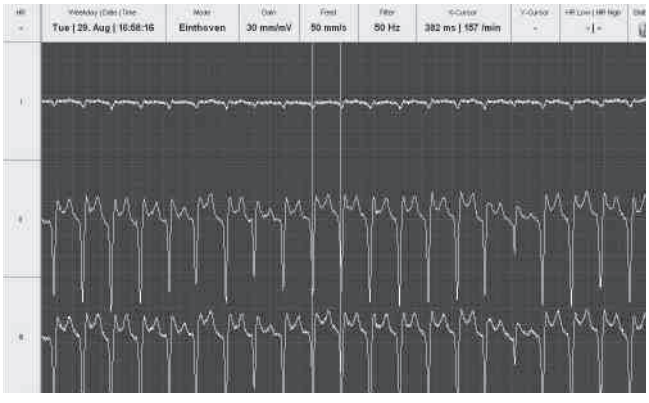

Fig. 3 With progression of the disease, the base-apex Holter ECG showed a further shortening of the RR-interval (382 ms, HR 157 bpm). A variable QRS amplitude (1 mV–2.5 mV) was noticeable.

Table 1 Left and right ventricular function

LV AMM FS	0.5 cm
LVEDV	304.85 ml
LVESV	37.04 ml
LVEF	87.84 %
LVST	67.4 ml
Lvecc d ch	1.1 cm
Lvecc s ch	1.2 cm
RV area/LV area d4ch	0.8 cm^2
RV area/LV area s4ch	0.7 cm^2
RVID/LVIDdM ch	0.3 cm
RVID/LVIDsM ch	0.25 cm
RV area FAC 4ch	0.7 cm^2
RV FAC left	0.66 cm^2

LV: left ventricle; AMM: anatomical motion-mode; FS: fractional shortening, LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume, Lveecc d ch: left ventricular end-diastolic eccentricity index at chordal level measured in short-axis view at chordal level; Lveecc s ch: left ventricular end-systolic eccentricity index at chordal level measured in short-axis view at chordal level; RV area/LV area d4ch: Ratio between end-diastolic right and left ventricular area measured in long axis four-chamber view; RV area/LV area s4ch: Ratio between end-systolic right and left ventricular area measured in long axis four-chamber view; RVID/LVIDdM ch: Ratio between end-diastolic right and left ventricular internal diameter measured in short axis-view at chordal level in M-mode; RVID/LVIDsM ch: Ratio between end-systolic right and left ventricular internal diameter measured in short axis-view at chordal level in M-mode; RV area FAC 4ch: right ventricular fractional area change measured in long axis four-chamber view calculated as (RV area d 4ch-RV area s4ch)/RV area d4ch × 100; RV area FAC left: right ventricular fractional area change measured in long axis left ventricular outflow tract view calculated as (RV area d left-RV area s left)/RV area d left × 100

bular injury most likely due to increased renal interstitial pressure in conjunction with output failure. Additionally, hepatic lipidosis was observed.

The lung showed a pronounced, diffuse, congestive hyperemia and severe, acute, alveolar edema.

Unfortunately, microbiological examination from freshly isolated heart tissue was not performed. Therefore, DNA was extracted from formalin-fixed myocardial tissue using a commercial kit. Multiplex Real Time PCR according to *Cordoni* et al. 2015 as well as qualitative eubacterial PCR according to *Nadkarni* et al. 2002 yielded negative results.

Discussion

Atrial standstill has not been previously described in donkeys. By definition, atrial standstill is a transient or persistent arrhythmogenic condition characterized by the complete or partial absence of electrical and mechanical activity in the atria (*De Clercq* et al. 2012).

From the outset, no P waves were detectable in the ECG of the donkey. Screening for glycosides showed high serum levels of digitoxin, the source of which remained obscure. Post mortem, histopathological examination showed that extensive parts of the atria had been destroyed. Most likely, glycoside intoxication with resulting myocarditis contributed to the cardiac syndrome observed in the donkey.

Initially, the QRS complexes had a normal appearance. Ventricular contraction was triggered by an irregular escape rhythm that was initially shaped as expected in horses, with a prominent negative S wave.

A further pathological feature of the ECG was the T-wave inversion, most likely caused by toxic digitoxin levels (Table 1). However, similar effects are also seen in the second phase of pericarditis, reflecting defects in the repolarization of the tissue near the pericard. In line with this, T-wave inversion disappeared in later ECG recordings in the present case (figure 2), as to be expected deeper myocardial layers are affected in the course of progression from peri- to myocarditis. Ventricular ischemia may have further contributed to the ECG abnormalities observed (*Hayden* et al. 2002). This hypothesis is in line with the significant increase of troponin I and alpha hydroxybutyrate dehydrogenase as markers of myocarditis. Furthermore, a novel cardiac resp. renal biomarker that is being studied in our clinic – namely symmetric dimethylarginine – showed an elevation. Asymmetric dimethylarginine, a human cardiac biomarker, was also highly elevated.

Apart from myocarditis, causes for atrial standstill include glycoside intoxication and hyperkalemia (*De Clercq* et al. 2012). While systemic hyperkalemia was at no time present in the donkey, serum digitoxin was elevated. Since iatrogenic exposure of the donkey to digitoxin could not be verified despite scrutiny, it appears

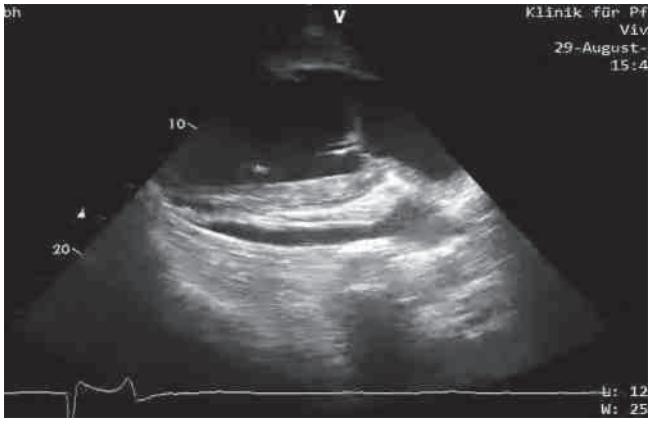

Fig. 4 Left parasternal long axis view with pericardial effusion.

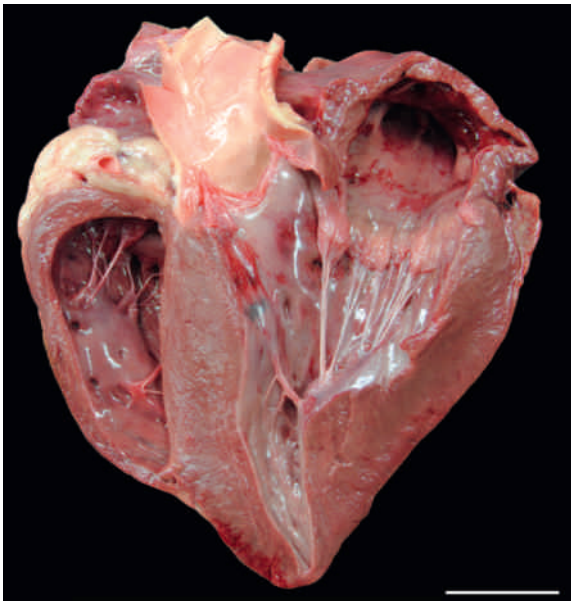

Fig. 5 Gross image of the longitudinal section of the heart with multifocal, subendocardial petechia in the ventricle and atria. Bar = 5 cm

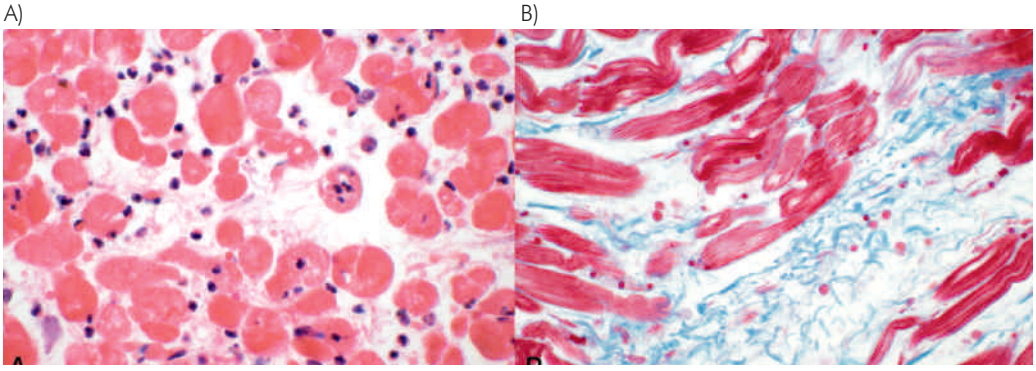

Fig. 6 A) Histopathological image of the atrial myocardium with moderate infiltration with neutrophilic granulocytes (purulent atrial myocarditis), hyaline degeneration of cardiomyocytes and intramuscular edema. H&E stain. Bar = 20 µm. B) Histopathological image of the atrial myocardium with multifocal deposition of collagen fibers (blue). Azan stain. Bar = 20 µm

possible to speculate that the intoxication might have been the result of ingestion of glycoside containing plants (e.g., oleander, rhododendron, foxglove, lily of the valley, etc.). Foxglove (digitalis) contains several cardioactive substances including digoxin, which is metabolized to digitoxin within the body. Foxglove intoxication gives a very distinct ECG pattern, including blocks, ventricular tachycardia, and ST-deviation, along with nephritis and colitis. However, the precursor digoxin was not measured in plasma and signs of colitis or findings of plant ingredients were absent in necropsy so that this possibility remains speculative.

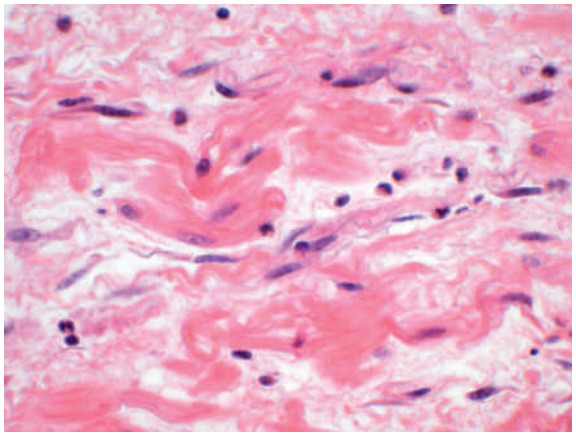

Fig. 7 Histopathological image of the sinoatrial node with mild infiltration with neutrophilic granulocytes. H&E stain. Bar = 20 µm

Due to parasympathetic action, cardiac glycosides have direct negative chronotropic and dromotropic effects (*De Clercq* et al. 2012). Furthermore, cardiac glycosides induce rises in cytosolic Ca^{2+} which enhance contractility at physiological dosages but have been implicated in glycoside-induced apoptisis with necrosis and inflammation of the myocardium in cases of intoxication (*Hayden* et al. 2002, *Galey* et al. 1996). This might explain the histological finding of myocarditis in the current case. Apart from toxic insults, causes for myocarditis include viral or bacterial infections, parasitic migration, fungal infections, nutritional imbalances,

Table 2 Laboratory results

	measured	reference range	reference
packed cell volume	49 %	31–43 %	donkey [*Garba* et al. 2015]
red blood cells	9.2×10^{12}/L	$4.4–7 \times 10^{12}$/L	donkey [*Burden* et al. 2016]
white blood cells	14.92×10^{9}/L	$3.5–10.9 \times 10^{9}$/L	donkey [*Garba* et al. 2015]
neutrophile granulocytes	12.9×10^{9}/L	$2.4–6.3 \times 10^{9}$/L	donkey [*Burden* et al. 2016]
glucose	260 mg/dL	69.1–82.9 mg/dL	donkey [*Garba* et al. 2015]
lactate	11.9 mg/dL	0.5–2.0 mg/dL	institutional reference range horse
PaO_2	52 mmHg	95–105 mmHg	institutional reference range horse
$PaCO_2$	60 mmHg	35–45 mmHg	institutional reference range horse
pH	7.28	7.34–7.44	institutional reference range horse
bicarbonate	19.5 mmol/L	21.7–26.3 mmol/L	donkey [*Garba* et al. 2015]
anion gap	29 mmol/L	9–17 mmol/L	institutional reference range horse
lactate dehydrogenase	527 U/L	> 400 U/L	laboklin laboratory
γ-glutamyl transferase	197 U/L	14–69 U/L	donkey [*Burden* et al. 2016]
aspartate aminotransferase	584 U/L	238–536 U/L	donkey [*Burden* et al. 2016]
creatinine	6.38 mg/dL	0.6–1.34 mg/dL	donkey [*Burden* et al. 2016]
blood urea nitrogen	185 mg/dL	27–93 mg/dL	donkey [*Burden* et al. 2016]
troponin I	50 ng/mL	> 0.03 ng/mL	laboklin laboratory
α-hydroxybutyrate dehydrogenase	290 U/L	> 170 U/L	laboklin laboratory
LDH/HBDH	2:1.1	2:1	laboklin laboratory
atrial natriuretic peptide	4558 pg/mL	2023–22714 pg/mL	institutional reference range horse
symmetric dimethylarginine	2.1 µmol/L	0.3–0.8 µmol/L	DLD diagnostica GmbH
asymmetric dimethylarginine	9.0 µmol/L	1.7–3.8 µmol/L	DLD diagnostica GmbH
metanephrine	459 pg/mL	9.3–186.1 pg/mL	institutional reference range horse
normethanephrine	585 pg/mL	40.1–324.4 pg/mL	institutional reference range horse
triglyceride	430 mg/dL	20.0–144.0 mg/dL	donkey [*Dugat* et al. 2010]
vitamin E	8.4 mg/L	> 1 mg/L	laboklin laboratory
selen	92 µg/L	50–150 µg/L	laboklin laboratory
digoxin	< 0.5 µg/L	<0.5 µg/L	IDEXX laboratories
digitoxin	28.6 µg/L	<0.5 µg/L	IDEXX laboratories

PaO_2: partial pressure of oxygen in arterial blood, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, LDH: lactate dehydrogenase; HBDH: α-hydroxybutyrate dehydrogenase

hyperthermia, hypoxia, immune mediated and idiopathic disorders for which we had no evidence (*van Loon* 2012, *Breuhaus* 2011).

With ongoing disease, the donkey developed ventricular tachycardia. This change to ventricular tachyarrhythmia is a consequence of low output failure due to bradycardia and the progressive reduction in cardiac output, undoubtedly caused both by cardiac tamponade due to increasing pericardial fluid accumulation and direct myocardial damage. Hypoxemia can lead to local hyperkalemia (*Carmeliet* 1999), inducing hyperexcitability with ectopic generation of action potentials. Both hypoxia (*Hammarstrom* and *Gage* 2002) and concomitant acidosis (*Jones* et al. 2014) can interfere with the function of cardiac ion channels (*Carmeliet* 1999, *Hammarstrom* and *Gage* 2002, *Jones* et al. 2014), leading to increased excitability of cardiac tissues.

When digoxin toxicity is suspected, dioxin immune Fab fragments (antibodies) are given to human patients (*Higgins* et al. 1989). Furthermore, treatment with activated charcoal and laxatives via nasogastric tube may be beneficial to clear the intestine and prevent further absorption of glycosides.

Less specific but essential measures include management of acidosis and anticoagulant treatment. Patients with bradycardia due to atrial standstill can benefit from sympathomimetic agents or vagolytic agents, although sympathomimetics may enhance tissue excitability and promote reentry phenomena (*McGuirk* and *Muir* 1985, *Bonagura* et al. 2010, *Davey* 1986). For this reason, implantation of a pacemaker is usually preferable (*van Loon* et al. 2002, *Pibarot* et al. 1993, *Reef* et al. 1986). In the current case, emergency pericardiocentesis might have been tried, however, it is highly unlikely that either this or implantation of a pacemaker would have changed the prognosis of the severely ill patient.

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