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Clinical Report

Takotsubo Cardiomyopathy-like Transient Systolic Dysfunction in Two Bald Eagles (*Haliaeetus leucocephalus*)

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Abstract: Two wild adult bald eagles (*Haliaeetus leucocephalus*) were presented to the University of Florida zoological medicine department on separate dates, both being unable to fly. One eagle had a fracture of the left humerus, and the second had no external injuries. Thoracic radiographs of both animals revealed cardiomegaly, and echocardiography revealed reduced systolic function. Both eagles were treated with oral pimobendan until recheck echocardiography documented normal systolic function. Several weeks after pimobendan was discontinued, the echocardiograms of both eagles showed normal systolic function and were considered normal. The transient nature of systolic dysfunction in these 2 eagles could be consistent with a stress-induced, Takotsubo cardiomyopathy-like phenotype although traumatic myocarditis or adverse anesthetic reactions must also be considered.

Key words: Takotsubo cardiomyopathy, echocardiography, cardiology, anesthesia, avian, bald eagle, *Haliaeetus leucocephalus*

CLINICAL CASES

Case 1

A wild adult bald eagle (*Haliaeetus leucocephalus*) of unknown sex was presented to the University of Florida Zoological Medicine Service (Gainesville, FL, USA) for evaluation after being found on the ground in Putnam County, FL. The eagle had an ideal body condition score of 3/5 and muscle condition score of 3/3. Examination revealed an open oblique left mid-humeral fracture and active bleeding. There was no evidence of electrocution. Thoracic auscultation was normal with no murmur or arrhythmia appreciated. The eagle was given supportive care and pain management, including meloxicam (0.2 mg/kg PO q12h × 2 days, subsequently increased to 1 mg/kg PO q12h × 44 days; Metacam, Boehringer Ingelheim Vetmedica Inc, St. Joseph, MO, USA), lactated Ringer solution (120 ml/kg subcutaneously once; Dechra, Overland Park, KS, USA), pentoxifylline (25 mg/kg PO q12h × 28 days; compounded in-house at the University of Florida Veterinary Hospital (UFVH) Pharmacy, Gainesville, FL, USA), enrofloxacin (10 mg/kg PO q12h × 36 days; compounded in-house at UFVH), and hydromorphone (0.2 mg/kg IM q12h × 5 days; Hikma, Cherry Hill, NJ, USA). Physical examination of the conscious eagle confirmed an oblique open left mid-humeral fracture. The patient was anesthetized with 5% isoflurane by facemask, intubated, and maintained on 2% isoflurane in 1.5 L/min oxygen, and the fracture was stabilized with an intramedullary pin and type I external fixation tie-in. Recovery from anesthesia was slow but uneventful.

One day after presentation, blood was collected for diagnostic testing, and the serum biochemistry panel revealed an elevated creatinine kinase (CK; 3801 U/L, reference interval 190–1000 U/L) and aspartate transaminase (AST; 1307 U/L, reference interval 131–962 U/L), consistent with musculoskeletal injury.[1] The complete blood count was within normal limits. Systemic lead concentrations were 10.2 μg/dL (reference interval <20 μg/dL).[2] Radiographic images of the patient following the surgical procedure confirmed proper reduction of the fracture and revealed an enlarged cardiac silhouette (heart 66% of thoracic size, normal 44%–52%), hepatomegaly, and coelomic effusion (Fig 1).[3] Additionally, a third heart sound (presumptive diastolic gallop) was appreciated on auscultation.

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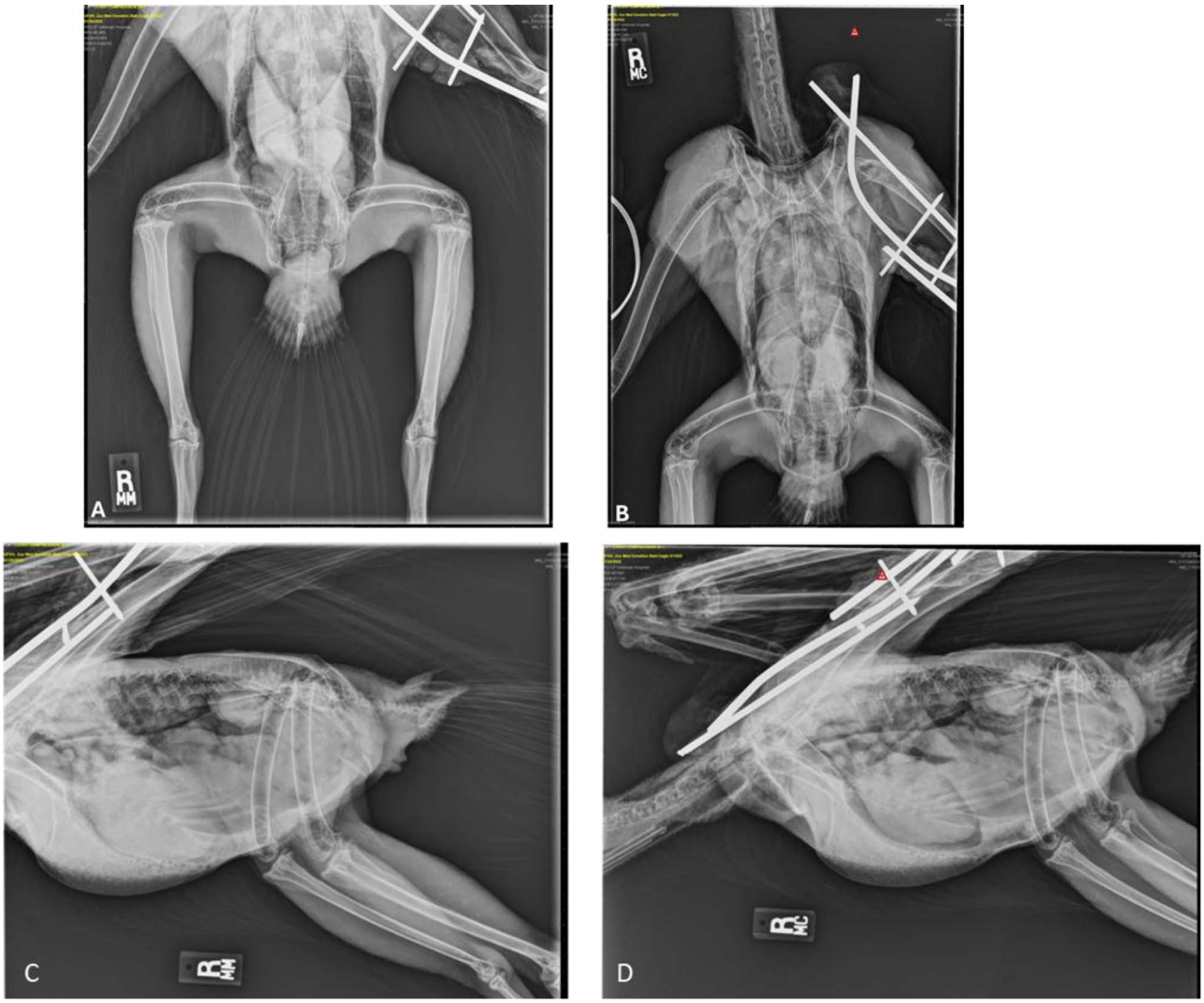

Figure 1. Case 1, (A) dorsoventral and (C) lateral radiographs of an adult bald eagle (*Haliaeetus leucocephalus*) demonstrating radiographic evidence of cardiomegaly (heart 66% of thoracic width; reference interval 44%–52%); (B) dorsoventral and (D) lateral radiographs demonstrating improved cardiomegaly approximately 6 days after initial diagnosis.

Two days after presentation, an electrocardiogram (ECG) revealed frequent atrial premature complexes with variable P-wave morphology and underlying sinus bradycardia (Fig 2) (patient heart rate 90–110 beats per minute [bpm], reference interval 150–220). Echocardiography was performed to further evaluate hepatocardiomegaly and arrhythmia. All measurements were obtained from 2-D and Doppler transthoracic echocardiography without M-mode due to limitations of avian anatomy. The patient was clinically affected enough not to require anesthesia or sedation and tolerated the cardiology examination with the use of a raptor hood and gentle restraint.

Echocardiography revealed subjective left-sided cardiomegaly with a left ventricular end-diastolic volume of 11.2 mL and generalized hypokinesis of the left ventricle with a decreased ejection fraction of 44% (compared with healthy eagles, n = 1, Table 1).[4] The right atrium and ventricle appeared normal in size compared with established reference intervals for diurnal raptors.[4] Right ventricular systolic function appeared subjectively decreased with an end systolic volume of 6.5 mL. The mitral valve was structurally normal with mild-to-moderate central mitral regurgitation present. Hepatic veins were prominent. The aortic and tricuspid valves appeared structurally normal, and the pulmonic valve could not be assessed. The findings were consistent with reduced systolic function compared with a normal, healthy bald eagle (Table 1). An underlying etiology was not identified, but consideration was given to trauma, electrocution, or myocarditis. A cardiac troponin I fluorescent immunoassay was submitted (University of Florida

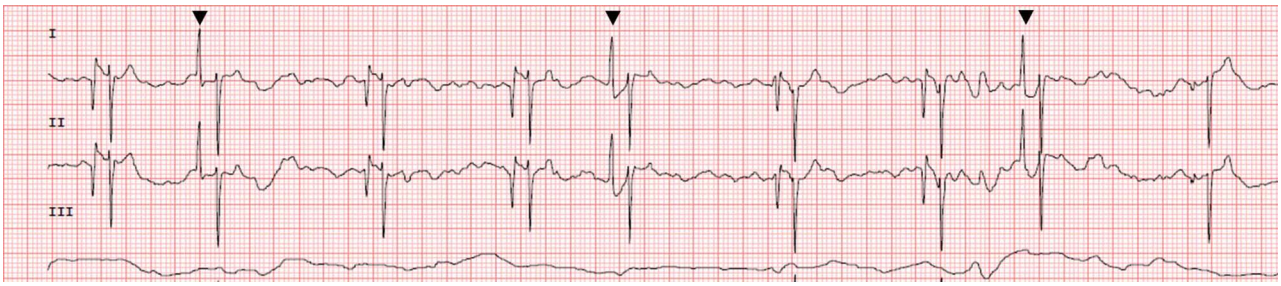

Figure 2. Electrocardiogram recordings (leads I, II, and III) obtained from the adult bald eagle (*Haliaeetus leucocephalus*) described in case 1 following isoflurane anesthesia. There is an underlying sinus bradycardia with a heart rate of approximately 110 beats/minute. The undulating baseline is secondary to movement artifact. There are 3 atrial premature complexes (arrowheads) with variable P wave morphology and a maximum coupling rate of approximately 187 beats/minute. Paper speed = 50 m/s; 1 cm = 1 mV.

Veterinary Clinical Pathology Laboratory, Gainesville, FL, USA) using the Triage cardiac panel (Quidel Cardiovascular Inc, San Diego, CA, USA), but the value was below the limit of detection. Therapy with pimobendan (0.67 mg/kg PO q12h × 3 days; Vetmedin; Boehringer Ingelheim Vetmedica Inc) was initiated.[5,6]

A recheck echocardiogram was performed 3 days later to assess the bird's response to medical therapy. Left ventricular end-diastolic and end-systolic volumes were smaller than the previous study at 7.5 and 2.1 mL, respectively. Ejection fraction was improved at 72%. Due to apparent improvement of systolic function, therapy with pimobendan was discontinued. An echocardiogram performed 3 days later confirmed normal systolic function and a normal sinus rhythm. Ejection fraction remained improved and subjectively normal at 69.14%. The patient remained in hospital for an additional 8 weeks until being transferred to a wildlife rehabilitation facility for future release.

Case 2

A wild adult bald eagle of unknown sex was presented to the University of Florida Small Animal Hospital after being found unable to fly. The eagle had an ideal body condition score of 3/5 and muscle condition score of 3/3. There was no evidence of electrocution, and the remainder of the external physical examination revealed no overt abnormalities. A serum biochemistry panel revealed an elevated CK (6279 U/L, reference interval 190–1000 U/L) and AST (1783 U/L, reference interval 131–962 U/L), supportive of suspected soft tissue trauma.[1] Lead concentrations were too low to read (<3.3 μg/dL). The eagle was anesthetized for radiographic imaging using 5% isoflurane in a 1.5 L/min flow of oxygen for induction, intubated, and maintained on isoflurane to effect with 1.5 L/min oxygen. The radiographic images revealed cardiomegaly (60% of thoracic cavity, reference interval 44–52%), but no fractures were detected (Fig 3).[3] Prophylactic anti-aspergillosis treatment was instituted with itraconazole solution (5 mg/kg PO q24h × 23 days; Elanco US Inc, Greenfield, IN, USA) and terbinafine HCl (20 mg/kg PO q24h × 23 days; Elanco).

Further imaging was performed to investigate the suspect cardiomegaly. The study was performed immediately following an uneventful patient recovery from the aforementioned anesthetic event. Poor left ventricular systolic function with an ejection fraction of 33% was identified through 2-D echocardiography.[4] There was no evidence of mitral valve regurgitation. A 6-lead ECG showed a second degree atrioventricular block with a sinus rate of approximately 170 bpm and ventricular rate of approximately 80 bpm (Fig 4). Cardiac troponin I concentration measured with a

Table 1. Echocardiographic measurements of the 2 described adult bald eagles (*Haliaeetus leucocephalus*) with Takotsubo cardiomyopathy-like transient systolic dysfunction at presentation and subsequent follow-up compared with values of a healthy control bald eagle.

	Case 1 initial	Case 1 follow-up	Case 2 initial	Case 2 follow-up	Healthy control bald eagle
End-diastolic volume, mL	11.2	7.5	17.7	6.5	9.0
End-systolic volume, mL	6.5	2.1	11.9	1.7	2.2
Ejection fraction, %	42.08	72.38	48.06	77.67	75.42

Abbreviations: mL, milliliters.

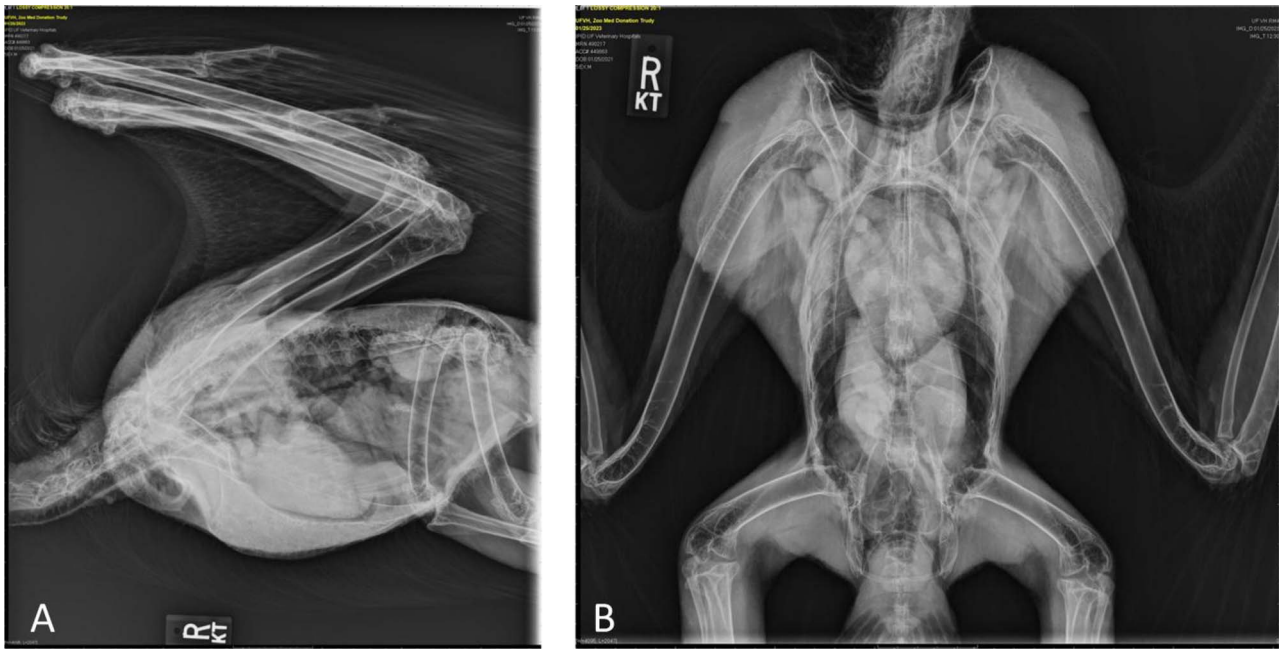

Figure 3. Case 2, (A) right lateral and (B) dorsoventral radiographs of an adult bald eagle (*Haliaeetus leucocephalus*) demonstrating radiographic evidence of cardiomegaly (heart 60% of thoracic width; reference interval 44%–52%) prior to apparent resolution.

chemiluminescence immunoassay was <2.5 pg/mL (Texas A&M University; College Station, TX, USA) using the Centaur Cardiac Troponin I TNI assay on the Advia Centaur CP system (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA), which is not elevated when compared with established ranges for other avian species (reference interval <0.16 pg/mL).[7] Therapy with pimobendan (0.7 mg/kg PO q12h × 15 days) was initiated.[5,6]

Another ECG was performed on the eagle 2 weeks later. The study was again performed without sedation or anesthesia and was well tolerated by the patient with gentle restraint and a raptor hood. The left ventricular cavity size and systolic function were both subjectively improved (Table 1). On 2-D echocardiography, the ejection fraction was found to be improved to 78%. Left ventricular outflow velocity was considered mildly elevated at 2.5 m/s but laminar, consistent with the patient's excitement. The left and right atria were subjectively normal in size, and the right ventricle showed subjectively normal systolic function. A 6-lead ECG and trace ECG throughout the echocardiogram revealed normal sinus rhythm. Based on the improvement of systolic function, pimobendan was discontinued.

One week later, repeat echocardiography showed that the left ventricular cavity size and systolic function remained unchanged (Table 1). Ejection fraction remained improved and subjectively normal at 74%. The ECG again revealed normal sinus rhythm. The study was performed without anesthesia, and the patient was again amenable to gentle restraint and a raptor hood. The eagle was determined to be suitable for release and remained in hospital for an additional week before it was transferred to a wildlife rehabilitation facility.

DISCUSSION

Cardiomyopathy has been described in raptors, but we were unable to find reports of temporary echocardiographic systolic dysfunction that resolved without the need for long-term cardiac medications. Given the rapid resolution and apparent lack of clinical signs related to cardiac dysfunction, secondary cardiomyopathy is prioritized over primary cardiomyopathy. It is possible that the systolic dysfunction might have been stress-induced cardiomyopathy (akin to Takotsubo cardiomyopathy or "broken-heart syndrome" in people), traumatic myocarditis, myocardial stunning, or secondary to recent anesthetic events using isoflurane.[8]

Takotsubo cardiomyopathy, or stress cardiomyopathy, is a well-described phenomenon in people in which there is a reversible reduced systolic function and ballooning of the left ventricle secondary to extreme physical or emotional duress.[9] Due to the association with stressful events, the most widely accepted mechanism is catecholamine-induced cardiotoxicity. Catecholamine-induced cardiotoxicity occurs

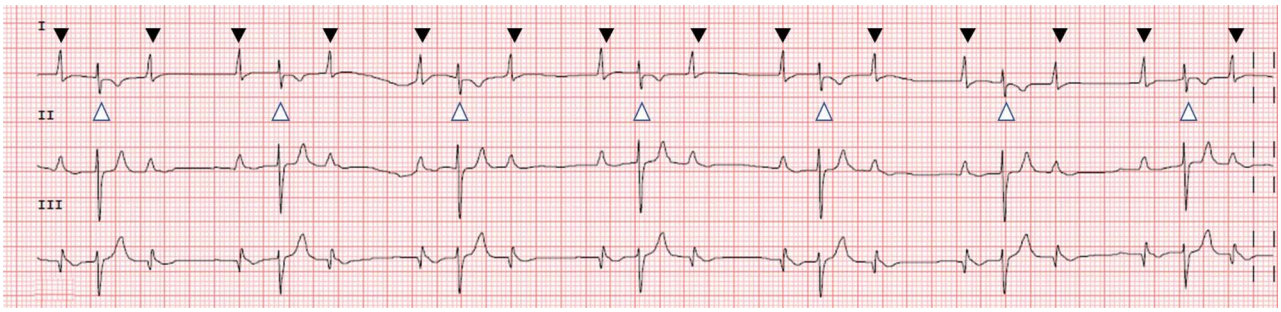

Figure 4. Electrocardiogram recordings (leads I, II, and III) obtained from the adult bald eagle (*Haliaeetus leucocephalus*) described in case 2 following isoflurane anesthesia. There is a 2:1 atrioventricular block with a sinus rate of approximately 170 beats per minute (black arrowheads) and a ventricular response rate of approximately 80 beats per minute (white arrowheads). Paper speed = 50 m/s; 1 cm = 1 mV.

via the beta-1 adrenoreceptor signal transduction pathway; the resulting overload of intracellular calcium in myocardial cells causes left ventricular dysfunction.[10] The revised Mayo Clinic criteria for diagnosis of Takotsubo cardiomyopathy are 1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegment with or without apical involvement (the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present); 2) the absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture; 3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or a modest elevation in cardiac troponin; and 4) absence of pheochromocytoma or myocarditis.[11] Patients with Takotsubo cardiomyopathy often have elevated plasma concentrations of epinephrine compared with patients with acute myocardial infarction secondary to coronary artery disease,[12] and similar phenotypes have been observed in people with pheochromocytomas and secondary to exogenous catecholamine administration.[10,12] After coronary artery disease has been ruled out, treatment consists of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and anticoagulants.[6] There are some reports of successful treatment with calcium channel sensitizers such as levosimendan, a drug with a similar mechanism to the pimobendan used in this report.[12] Spontaneous resolution often occurs within 1–3 months of initiating treatment,[10] and recovery rate is around 95%.[12] Although left ventricular hypertrophy has been described in some human patients with Takotsubo cardiomyopathy, it is considered an uncommon presentation.[13] Similar transient cardiac dysfunction secondary to stress has been described in other species, most notably cats, in the form of transient myocardial thickening. These cases present with a hypertrophic cardiomyopathy phenotype.[14] There has been a reported case of a stress-associated hypertrophic cardiomyopathy phenotype described in a red-necked wallaby (*Macropus rufogriseus*) although the wallaby died, so it was unknown whether the cardiomyopathy would have resolved.[15]

The low cardiac troponin I concentration in the eagle in which it was successfully measured does not support a diagnosis of traumatic myocarditis or myocardial stunning (a response to an ischemic event). Additionally, although elevated troponin is a diagnostic criterion for Takotsubo cardiomyopathy, concentrations are generally less elevated than in patients with coronary artery disease.[9,11] However, whereas cardiac troponin I is known to be highly conserved among mammalian species, it has not been validated in avian species. The results were within normal limits based on the limits of detection established in double-crested cormorants (*Nannopterum auritum*) although health could not be confirmed in this study population.[7] Moreover, whereas case 2 measured cardiac troponin I using the same methodology as the cormorant study, the assay used for the first case was different. It is, therefore, unlikely to have significant diagnostic value in these cases.

A case of a bald eagle with apparent resolution of systolic dysfunction has been previously published; however, the eagle likely had primary underlying cardiac disease.[16] That eagle was part of an educational program and was noted to have supraventricular premature complexes. The bird sustained physical trauma after flying into a pole approximately 4 months prior to examination. Computed tomographic angiography images revealed atherosclerosis, and echocardiography identified decreased left ventricular systolic function and left ventricular and atrial enlargement. The patient was treated with isoxuprine, pimobendane, and sotalol. When reexamined 8 months later, there was apparent resolution of both its arrhythmia and left atrial size. However, cardiac abnormalities were attributed to underlying atherosclerosis and the patient remained on medications long term, raising the possibility that trauma

was not the sole etiology. In contrast, the eagles described in our report recovered within several days to weeks and did not require long-term drug therapy.

The first eagle in this report had a known physical injury, and although the second bird did not exhibit external lesions, elevated CK and AST activities were suggestive of recent muscle injury. These findings may be supportive of a Takotsubo cardiomyopathy-like phenotype, which has been noted to occur secondary to physical trauma. However, traumatic myocarditis could not be ruled out because echocardiographic findings are nonspecific for myocarditis and include ventricular hypokinesis.[17] Additionally, both birds initially exhibited cardiac rhythm abnormalities consistent with previous clinical reports. Although the patients were not anesthetized for echocardiography, they both had recently undergone anesthetic events. Bald eagles seem to show a particular sensitivity to isoflurane anesthesia, and arrhythmias secondary to administration of isoflurane anesthesia have been described, including second degree atrioventricular block, atrial premature complexes, sinus tachycardia, T-wave depression, and sinus arrest.[8,18] In a study of 12 bald eagles anesthetized repeatedly with isoflurane as a sole anesthetic agent, 75% developed arrhythmias. These arrhythmias occurred most often during induction or recovery but resolved once the patients were anesthetized.[18] However, these eagles underwent significant stress prior to induction of anesthesia, including ECG lead placement, pressure cuff placement, temperature measurement, and blood sampling, which may have contributed to the development of arrhythmias. Stress-induced catecholamine release secondary to induction with anesthesia was also suggested as a mechanism for development of isoflurane-induced arrhythmias in bald eagles.[18] It is, therefore, possible that bald eagles develop systolic dysfunction as an adverse drug reaction to isoflurane but also that perianesthetic stress associated with induction results in cardiac dysfunction.

Echocardiographic reference intervals have not been established in bald eagles although there are published echocardiographic reference intervals for other diurnal raptors.[4] It is recommended to utilize species-specific reference intervals whenever possible. The echocardiographic values for the eagles presented in this case and the healthy eagle were larger with higher ventricular lengths than that of the previously reported diurnal raptors; therefore, the echocardiographic size should be interpreted with caution. Establishing echocardiographic reference intervals in bald eagles will allow for improved objective evaluation of cardiac function in this species, but in the absence of this information, we used an apparently healthy bald eagle for comparison when evaluating the echocardiographic findings for the injured eagles described in this report. An echocardiogram was performed on an adult female bald eagle resident of the Santa Fe Teaching Zoo (Gainesville, Fl, USA) as part of yearly health screening without anesthesia or sedation. On physical examination, the eagle had an ideal body condition score of 3/5 and muscle condition score of 3/3. Cardiac auscultation revealed no overt abnormalities. The eagle had an ejection fraction of 75%, end-diastolic volume of 9.0 mL, and end-systolic volume of 2.2 mL. The ECG revealed a normal sinus rhythm with a heart rate of approximately 220 bpm. No echocardiographic abnormalities were noted, and therefore, this patient was used as a healthy control for the previously described cases. Table 1 summarizes the echocardiographic findings for the healthy eagle as well as the injured eagles. Due to their status as a protected species, there is a limited population of apparently healthy captive eagles available for comparison, and only one apparently healthy eagle was available as a control.

Treatment with oral pimobendan was initiated in both eagles due to its positive inotropic effects. Beta blockers, although commonly used in human patients with cardiac disease, are considered contraindicated in animals due to negative inotropic and chronotropic effects. There are no established dose ranges for pimobendan in all avian species with reported doses ranging from 0.25 to 10 mg/kg.[5,6] In a pharmacokinetic study of pimobendan dosed at 10 mg/kg in Hispaniolan parrots (*Amazona ventralis*), peak plasma concentration was similar to that of dogs dosed at 0.25 mg/kg.[5] However, a report of pimobendan used at the same dose in a Harris hawk (*Parabuteo unicinctus*) had peak plasma concentrations several times higher, and a 0.25 mg/kg dosage resulted in peak plasma concentration closer to therapeutic concentrations.[6] The doses administered to these eagles were extrapolated from this data; however, further evaluation of the pharmacokinetics of pimobendan in bald eagles must be performed to identify an effective dose range for this species.

This report describes the clinical presentation, diagnosis, treatment, and outcome of transient systolic dysfunction in two bald eagles. The clinical course of these 2 eagles is consistent with Takotsubo cardiomyopathy described in humans and might have been either secondary to physical injury or the stress of handling and anesthesia. Other causes of transient myocardial dysfunction, such as adverse anesthetic reactions or traumatic myocarditis, were not completely ruled out in these eagles. Cardiomyopathy may be under-recognized in bald eagles, and the transitory

nature of cardiomyopathy in these cases indicates that it may not preclude release. This report highlights the need for awareness of potential stressors, especially when performing cardiac evaluation on anesthetized eagles, as well as the need for continued cardiac monitoring in bald eagles undergoing rehabilitation because of the potential for cardiac recovery.

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