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Successful Treatment of Idiopathic Dilated Cardiomyopathy in an Adult Chimpanzee (*Pan troglodytes*)

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Various congenital and acquired forms of heart disease have been reported in captive lowland gorillas, and heart disease is a major cause of morbidity and mortality in geriatric humans. However, the prevalence of heart disease is unknown in nonhuman great apes species. Indeed, little is known about heart disease in chimpanzees, although the species has been used in research for decades. This report details the clinical presentation and diagnostics (thoracic radiography, electrocardiography, and echocardiography) utilized to diagnose idiopathic dilated cardiomyopathy in a 27-year-old male chimpanzee. Treatment decisions—indicated by followup diagnostics including repeat electrocardiography, echocardiography, and clinical laboratory data—over the 22-month period during which he continues to be treated are described. In addition, electrocardiographic and echocardiographic findings obtained from 20 clinically normal adult (11 female and 9 male) chimpanzees are presented for comparison.

There are few published data regarding the prevalence of cardiovascular disease in chimpanzees. It is possible cardiac disease in older chimpanzees will become more apparent as chimpanzees live to older ages in captivity and the research environment (5). Early recognition and correct diagnosis of cardiovascular disease is critical if efforts to manage it are to be successful. Furthermore, to enable appropriate assessment and treatment, normal cardiac ranges must be elucidated for the species.

Myocardial fibrosis and congestive heart failure has been reported in an adult male chimpanzee (7). However, this single report regarding cardiovascular status in chimpanzees is surprising considering the larger number of reports of cardiovascular disease in lowland gorillas. Various congenital and acquired cardiovascular diseases have been recognized in captive lowland gorillas (9, 10, 19, 21), and cardiovascular disease is reported to be responsible for 41% of deaths in adult gorillas (15). A survey of our current chimpanzee colony from 1990 to 2000 listed cardiovascular disease as cause of death in the majority of cases (11). The prevalence of heart disease in humans is reported to rise from 1.0% for those 25 to 54 years of age to 4.5% for 65- to 74-year-olds (18).

In human beings, cardiac disease is associated with multiple risk factors including systemic hypertension (6). Systemic hypertension has been associated with sodium intake in the chimpanzee (2) and has occurred concurrently with heart disease in the gorilla (16). However, a possible association of high blood pressure with heart disease has not been evaluated in the chimpanzee.

Until now, standard echocardiographic reference values have not been established that would enable clinicians to evaluate cardiovascular health in captive or research chimpanzees. The purposes of this report are to present a case demonstrating the successful management of severe congestive heart failure (CHF) secondary to idiopathic dilated cardiomyopathy (DCM) in an adult male chimpanzee and to present cardiovascular parameters obtained from 20 of his clinically normal cohorts.

In November 2002, Abraham, a 27-year-old, captive-born male chimpanzee, was found to be severely exercise-intolerant and dyspneic post-exercise; an intermittent cough also was noted. In fact, his activity was so severely reduced that ischial decubital ulcers were detected upon closer observation. His mucous membranes were visibly cyanotic, and abdominal distension was observed by the attending veterinarian. Abraham had a history of mild systemic hypertension, for which he had been treated with an angiotensin converting enzyme inhibitor (lisinopril; 20 mg once daily) for approximately 1.5 years beginning in April 1999. However, the lisinopril was discontinued on a trial basis in September 2001, and his blood pressure remained normal. Thoracic radiographs taken at that time, however, revealed moderate left ventricular enlargement. In November 2002, a tentative diagnosis of CHF was made in light of his history of systemic hypertension and his clinical presentation as described earlier. From September 2001 until developing clinical signs suggestive of CHF in November 2002, Abraham was receiving no cardiac medications.

Because of the risks associated with general anesthesia for a complete physical examination and cardiac evaluation in an animal with overt CHF, medical therapy was initiated to address congestion without further diagnostics. Abraham was begun on 1.7 mg/kg furosemide (a loop diuretic) once daily; however clinical signs did not improve appreciably after 1 week of therapy. Therefore, lisinopril therapy was reinstituted at a dose of 0.25 mg/kg (20 mg/day), and furosemide was increased to 1.7 mg/kg twice daily the following week. His clinical demeanor improved,

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with increased mobility and less dyspnea after exercise, however his pronounced abdominal distension remained unchanged. Therefore, triple diuretic therapy was initiated 2 weeks after the addition of lisinopril and the increase in furosemide to better control his CHF to better control his CHF, with the goal of stabilizing him clinically in order to perform a complete cardiac evaluation. Hydrochlorthiazide, a thiazide diuretic (1 mg/kg once daily) and spironolactone, an aldosterone antagonist (1 mg/kg once daily), were added to his treatment protocol. These two pharmacologic agents, in conjunction with furosemide, make up the most common triple diuretic protocol used in veterinary cardiology. To minimize the risk of dehydration, furosemide was reduced to 1 mg/kg twice daily, and additional flavored oral liquid was offered several times daily to encourage water consumption, although he appeared to be drinking and eating normally.

Clinical signs improved enough to allow general anesthesia (tiletamine hydrochloride–zolazepam; 3.5 mg/kg) for a complete physical examination (PE), a complete blood count and chemistry panel, electrocardiogram (ECG), and echocardiogram in December 2002 (the week after beginning triple diuretic treatment). The PE confirmed the observations in the non-anesthetized patient. Prominent jugular distension was noted, and heart sounds were mildly muffled. Clinical laboratory findings were normal, with the exception of hypoalbuminemia (2.7 g/dl; normal range, 3.2 to 4.2 g/dl), hypokalemia (2.6 mEq/liter; normal range, 3.1 to 4.0 mEq/liter), mild azotemia (blood urea nitrogen [BUN], 38 mg/dl; normal range, 8 to 18 mg/dl, and elevated creatinine 1.6 mg/dl; normal range, 0.7 to 1.3 mg/dl). Abdominocentesis was performed, and 900 ml of transudate was removed. The ECG revealed a sinus rhythm with a heart rate of 80 beats per minute (bpm), and a brief echocardiogram revealed moderate cardiomegaly with severely reduced systolic function. These findings were consistent with a diagnosis of idiopathic DCM and secondary CHF. Therefore, digoxin (0.005 mg/kg twice daily), because of its positive inotropic effect, was added to the therapeutic protocol. The attending veterinarian also added terbutaline, a beta-adrenergic agonist (0.01 mg/kg twice daily), to the treatment protocol for the drug's bronchodilatory effects.

A complete re-exam was performed in April 2003, 6 months after these therapeutic changes. Physical examination at that time revealed Abraham to be bright, alert, responsive, and eupneic at rest, and the decubital ulcers had resolved. His mucous membranes were pink and moist, with prompt capillary refill time. Heart sounds remained muffled with no auscultable murmurs, but pulse quality was weak. A complete blood count and chemistry panel remained normal, with the exception of persistent mild azotemia (BUN, 22 mg/dl; creatinine, 1.6 mg/dl), hypercalcemia (11.1 mg/dl, normal range, 8.4 to 10.1 mg/dl), and hypokalemia (2.8 mEq/L). Thoracic radiographs revealed left ventricular enlargement that was similar to previous radiographs. The echocardiogram confirmed significant left heart enlargement with reduced left ventricular wall thickness. Systolic function was severely reduced, and mild mitral regurgitation and aortic insufficiency were noted with color flow Doppler. These findings are consistent with the previous diagnosis of DCM. His echocardiographic data is presented in Table 1, and Fig. 1 demonstrates a comparison of his M-mode echocardiogram (with poor left ventricular wall motion and left ventricular enlargement) to an M-mode tracing obtained from a clinically normal chimpanzee. Figure 2 shows a two-dimensional echocardiogram of Abraham's left ventricular outflow tract. Terbutaline therapy was discontinued in light of the lack of evidence suggesting that Abraham had airway disease in addition to heart disease, however, all other medications (digoxin, triple diuretic therapy, and lisinopril) were continued.

One year from diagnosis (November 2003), cautious alpha and beta blockade was initiated with carvedilol (0.03 mg/kg [1.56 mg] once daily) because Abraham's cardiac function appeared stable. This medication was chosen for the potential cardio-protective benefit of beta-blockade in chronic heart failure. However when after 1 week the drug was titrated upward to 3.125 mg once daily (0.06 mg/kg), his capacity for activity became markedly reduced, and carvedilol therefore was discontinued at that time. In February 2004, carvedilol was reinstituted at the lower dose uneventfully, and he has remained on this dose to date. Almost 2 years after initial diagnosis, Abraham continues to be eupneic at rest with modest exercise tolerance, and he is still the alpha male in his group. His ascites has remained controlled. A cardiac reevaluation in April 2004 revealed no overt signs of CHF despite severe DCM. Clinical laboratory findings at this time were consistent with worsening azotemia (BUN, 21 mg/dl; creatinine, 2.0 mg/dl), hypercalcemia (11.7 mg/dl), and hyperkalemia (4.8 mEq/liter), however other parameters remained within normal limits. The ECG revealed occasional atrial premature complexes and occasional multiform ventricular premature complexes with an underlying sinus rhythm. Furosemide was lowered to 0.5 mg/kg in the morning and 0.25 mg/kg in the evening because he consistently has no evidence of CHF (ascites or resting dyspnea) and azotemia had worsened. He is now on a yearly cardiac reexam program and continues to do well clinically.

Materials and Methods

All chimpanzees are maintained in group housing and fed commercial primate diet (Purina LabDiet Monkey Diet Jumbo #5037) (St. Louis, Mo.). They are maintained and used in accordance with the *Guide for the Care and Use of Laboratory Animals* (17). The facility and program are accredited as "exemplary" by the Association for Assessment and Accreditation of Laboratory Animal Care, International. Each chimpanzee participates in enrichment programs, with daily observation. All individual chimpanzees are observed several times daily by trained, experienced animal care technicians as well as staff veterinarians. The animals are observed for appetite, elimination, exercise tolerance, and exercise recovery rate. Each animal is anesthetized (tiletamine hydrochloride–zolazepam; 3.5 mg/kg [50 mg/cc of tiletamine HCL andzolazapam HCL]) yearly for a complete PE, complete blood count and chemistry panel, ECG, abdominal ultrasound, tuberculosis testing, dental prophylaxis, and blood pressure assessment. Positive reinforcement training has been initiated to permit unanesthetized examination under protected conditions. Blood pressure measurements, ECG, SpO_2, and core body temperature are recorded using a Datascope Passport 2 (Mahwah, N.J.) monitoring device. The electrocardiogram is monitored visually on the oscilloscope throughout anesthesia, and a 30-sec representative strip is permanently recorded for each individual. During these routine examinations, 20 clinically normal individuals underwent complete echocardiograms (including Doppler) with an Aloka Prosound 5000 (Tokyo, Japan) and a 2.5-mHz transducer to generate echocardiographic values for clinically normal adult chimpanzees.

Table 1. Echocardiographic parameters in normal adult, geriatric chimpanzees and Abraham (chimpanzee with dilated cardiomyopathy)

	Female (n = 11)	Male (n = 9)	Abraham
Body weight (kg)	55.0 ± 12 (38–66)	66.0 ± 19 (50–104)	54.3
Age (years)	24.0 ± 12.2 (12–45)	25.2 ± 7.7 (19–41)	27
Left ventricular internal diameter during diastole (mm)	39.3 ± 3.7 (36–42)	48.1 ± 6.3 (43–61)	69
Left ventricular internal diameter during systole (mm)	23.3 ± 3.9 (21–30)	29.9 ± 5.3 (24–37)	60
Shortening fraction (%)	40.8 ± 8.0 (33–50)	37.8 ± 7.9 (26–47)	13
Left ventricular internal diameter during systole (mm)	9.8 ± 1.3 (9–12)	11.2 ± 1.0 (9–13)	9
Left ventricular free wall diameter during diastole (mm)	10.5 ± 1.3 (9–13)	12.4 ± 1.6 (10–15)	8
aortic root diameter (mm)	23.9 ± 3.5 (20–30)	24.7 ± 2.7 (22–28)	31
Left atrial diameter (mm)	32.0 ± 5.3 (28–40)	30.2 ± 3.8 (26–36)	43
left atrial diameter/aortic root diameter	1.3 ± 0.3 (1.0–1.7)	1.3 ± 0.1 (1.1–1.4)	1.4
Peak flow velocity of the pulmonary artery outflow (m/sec)	0.9 ± 0.2 (0.6–1.1)	1.1 ± 0.1 (0.9–1.2)	0.7
Peak flow velocity of the aortic outflow (m/sec)	1.1 ± 0.2 (0.6–1.5)	1.1 ± 0.2 (0.7–1.2)	1.1

Data are presented as the mean ± SD, with the range in parentheses.

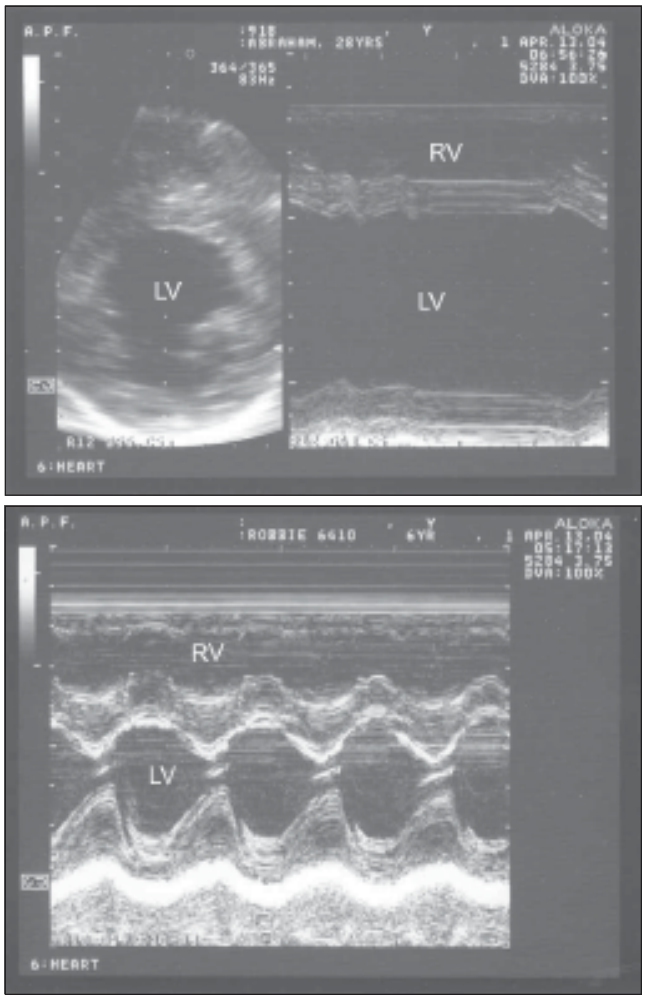

Figure 1. M-mode echocardiograms from Abraham (A) and a normal chimpanzee (B). The left frame of (A) is a two-dimensional image showing the ventricular level at which the M-mode tracing (right frame) is obtained. In an M-mode tracing, all cardiac structures along the cursor line drawn through the ventricles are displayed on a time line (x axis of the M-mode). Note the more vigorous ventricular motion and the smaller heart size in the normal chimpanzee (B) compared with Abraham (A). LV, left ventricle; RV, right ventricle.

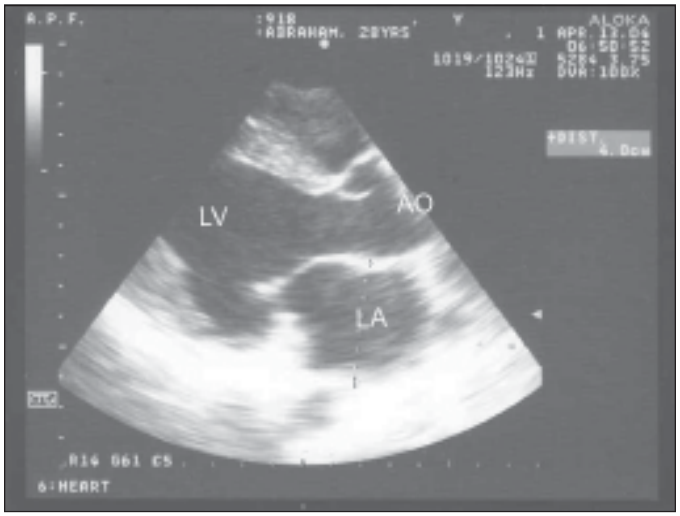

Figure 2. Echocardiogram from Abraham, showing the left ventricular outflow tract in the long axis. The mitral valve is mildly thickened and closed, and the aortic valve is open (systolic view). LV, left ventricle; LA, left atrium; AO, aorta.

Results

Echocardiographic results from 20 chimpanzees deemed to be clinically normal in light of PE findings are presented in Table 1. Abraham's echocardiogram, which revealed severe heart enlargement and decreased systolic function (evidenced by a reduced shortening fraction), is also presented in Table 1. The shortening fraction, a parameter of systolic function, was calculated using the following equation:

{[Diameter of left ventricle during diastole – diameter of left ventricle during systole] ÷ diameter of left ventricle during diastole} × 100.

Dysrhythmias occurred in two of the clinically normal chimpanzees. Both had single, uniform ventricular premature complexes; one of these individuals also had aberrant conduction (right bundle branch block), whereas the other demonstrated a wandering pacemaker. An additional chimpanzee with a sinus rhythm had a partial right bundle branch block (RBBB). The average heart rate for the males was 87 bpm (range, 60 to 110 bpm), whereas the average heart rate for the females was 107 bpm (range, 70 to 124 bpm).

Discussion

This report demonstrates marked clinical improvement in an adult, male chimpanzee with DCM and CHF after initiation of appropriate medical therapy. Decubital ulcers were resolved, and no signs associated with CHF remained at rest, consistent with notably improved quality of life. His exercise capacity and tolerance improved markedly, his resting respiratory pattern was normal, and no abdominal distension was visible. Treatment has continued successfully for 22 months after initial recognition of CHF.

To our knowledge, the present report is the first of successful medical management of heart disease in the chimpanzee. Therapy was similar to what would be used in a dog, cat or human with DCM and CHF and included preload reduction (diuretics), afterload reduction (lisinopril), and inotropic support (digoxin). Alpha and beta blockade was added to protect the heart from chronic elevated sympathetic stimulation and is used in veterinary and human cardiac patients with DCM. Upward titration must be cautious because beta blockers have a negative inotropic effect and can lead to worsening clinical signs (as seen with Abraham).

Echocardiography is the most commonly used, non-invasive diagnostic tool in veterinary and human cardiology, allowing assessment of chamber size, valvular anatomy, and myocardial function. However, echocardiography has not been performed routinely in chimpanzees, and therefore echocardiographic normal ranges have been previously unavailable. This report presents the echocardiographic data obtained from 20 clinically normal adult chimpanzees. Results of cardiac measurements were proportionally similar to those for human beings and those presented from assessment of five adult male gorillas (9). Trivial valvular regurgitation was apparent in some (n = 3) of the chimpanzees deemed clinically normal, however none of them had auscultable murmurs on PE.

Dysrhythmias (single ventricular premature beats) occurred in two of the chimpanzees judged to be clinically normal: one abnormality in conjunction with RBBB, and the other with wandering pacemaker. Wandering pacemaker has been recognized as occurring occasionally in clinically normal chimpanzees, and RBBB is considered a normal variant in many monkey species (rhesus, cynomolgus, and spider) (3); however we do not believe that RBBB has been previously recognized in a chimpanzee. There are many possible underlying etiologies for ventricular ectopy in this population of chimpanzees, which has been retired from various research protocols. Therefore, without further study of other populations, it is difficult to ascertain whether this prevalence of dysrhythmias would be expected in normal captive adult chimpanzees. The fact that ECGs were performed under anesthesia probably was not a factor. Anesthesia with tiletamine hydrochloride–zolazepam was not associated with arrhythmia genesis in 12 macaques (1). Moreover, in a study evaluating ECGs in five lowland gorillas anesthetized with tiletamine hydrochloride–zolazepam (14), none had ventricular rhythms in 12-lead ECGs. Although ECG assessment in three normal chimpanzees (two females and one male under ketamine–valium–xylazine anesthesia) did not reveal any arrhythmias, one of the gorillas had a supraventricular rhythm deemed not to be sinus in origin under ketamine–valium–xylazine anesthesia (4). However, the duration of the ECG was not described in these reports and therefore occasional dysrhythmias could have been missed if the evaluation was short.

Several of the chimpanzees in the current study are seropositive for various viral agents (hepatitis B and C, simian immunodeficiency virus). In addition, Coxsackie virus infection has been documented in chimpanzee neonates at the facility and in one exposed human involved with the colony (12). Various viral diseases have been associated with myocarditis in other species and could be a factor in dysrhythmia formation in this group, although their hearts appeared structurally normal on echocardiography. Finally, underlying unrecognized metabolic disease could also be a factor. The complex dysrhythmias evident in Abraham's ECG (multiform ventricular and atrial premature complexes) are not surprising given the severity of his structural heart disease.

A challenge to therapy in the chimpanzee is the necessity of general anesthesia for definitive diagnosis and assessment of therapeutic response. This need has been a leading factor limiting our ability to assess therapy; however with astute monitoring, therapy can still be effective, as seen in Abraham's case. The primary goal of therapy is to control signs of CHF without producing secondary dehydration and azotemia. Chimpanzees at this colony, including Abraham, are being trained with positive reinforcement to present at the side of their enclosure for auscultation and examination purposes. This training, when successful, will greatly enhance therapeutic monitoring.

Limitations of this study include the small sample size for the clinically normal chimpanzees (total of 20 adults) and the fact that these chimpanzees had participated in various research projects. It is possible that previous exposures may have led to cardiac changes that would not be present in a wild or zoo population of chimpanzees. However, regardless of the cause, cardiomyopathies have been recognized in multiple primate species, and this report describes successful therapy of CHF caused by DCM in a chimpanzee. In addition, although the presence of dysrhythmias may be associated with previous exposures in past research projects, the echocardiographic parameters in clinically normal patients are unlikely to be affected. There has been an increase in the morbidity and mortality associated with cardiovascular disease in the past two decades in the captive chimpanzee population (13), and it has been documented that cardiovascular disease is the major cause of death (8). In December 2000, Congress passed the Chimpanzee Health Improvement, Maintenance, and Protection Act (Public Law 106-551). This legislation provides funding for the life-long care of former research chimpanzees. Therefore, in the future there will be an increasing geriatric population, and the diagnosis and treatment of cardiovascular disease will be essential to a good health care program.

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