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Diagnosis and Treatment of Pulmonary Arterial Hypertension and Atrial Fibrillation in an Adult Chimpanzee (*Pan troglodytes*)

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This report describes the diagnosis and treatment of pulmonary arterial hypertension (PAH) in an adult male captive chimpanzee. Although cardiovascular disease in general is common in human and great apes, diagnosis and treatment of PAH in nonhuman primates are uncommon. In the case we present, the adult chimpanzee was diagnosed with an arrhythmia during an annual physical examination and later with PAH during a scheduled cardiovascular evaluation. PAH can either be primary or secondary and can lead to right ventricular overload and heart failure. This description is the first case study of pulmonary arterial hypertension in a great ape species.

Abbreviations: ECG, electrocardiogram; PAH, pulmonary arterial hypertension

Cardiovascular disease in captive chimpanzees (*Pan troglodytes*) has long been noted to be a leading cause of morbidity and mortality.[5,9,17] However, little has been written about the diagnosis and treatment of specific cardiac diseases in this species. Because chimpanzees are susceptible to acquired heart disease, a thorough cardiac evaluation is crucial for their medical management.

Cor pulmonale (right heart failure) refers to the changes in right ventricle structure and function that occur secondary to a respiratory disorder. Right heart failure occurs because of the increased pulmonary vascular resistance. In humans, pulmonary arterial hypertension (PAH) is defined as systolic pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise[8] and can lead to right ventricular overload and heart failure. In addition to causing right ventricular hypertrophy due to pressure overload, the increased arterial pressure can lead to extensive pulmonary vascular damage and consequently decreased oxygen and carbon dioxide transfer. Reversibility of these vascular changes is variable, poorly defined, and depends on the severity and duration of disease.[1]

Pulmonary arterial hypertension can be primary or secondary. Primary PAH is inherited in humans and results from an obliterative pulmonary arterial disease involving small and medium pulmonary arteries.[2] Secondary PAH can result from numerous metabolic and respiratory conditions, including respiratory diseases such as chronic obstructive pulmonary disease, interstitial lung disease, and pneumonia or pulmonary neoplasia. A common cause of PAH in dogs is heartworm disease, whereas pulmonary embolism is a common cause of the syndrome in humans.

Stump-tailed macaques (*Macaca arctoides*) have been evaluated for their suitability as an animal model for pulmonary hypertension.[18] This syndrome has been induced experimentally in baboons (*Papio anubis*) and stump-tailed macaques.[3,4] In addition, some rhesus macaques (*Macaca mulatta*) infected with recombinant SHIV *nef* virus developed PAH.[12,13] In the early 1970s cardiovascular and respiratory diseases were noted to be common in the captive chimpanzee population.[16] However, no current reports describe experimentally induced or spontaneous PAH in captive chimpanzees.

Case Study

In January 2004, a 22-y-old, 70-kg, captive-born male chimpanzee (*Pan troglodytes*) negative for hepatitis C, hepatitis B, and HIV viruses at the Alamogordo Primate Facility had multiform premature ventricular complexes (Figure 1) and hepatomegaly on a routine annual physical examination. Additional pertinent findings included an oxygen saturation of 75% in the absence of oxygen supplementation and blood pressure of 125/74 mm Hg (systolic/diastolic). Enlargement of the right side of the heart had been noted on previous radiographs, but no clinical signs of cardiovascular disease had been noted previously.

Each animal at the Alamogordo Primate Facility annually receives a complete physical examination under anesthesia (tiletamine hydrochloride–zolazepam, 3.5 mg/kg [50 mg/ml tiletamine HCl and zolazepam HCl]) and complete blood count, clinical chemistry, electrocardiogram (ECG), abdominal ultrasound, tuberculosis testing, dental prophylaxis, and blood pressure assessment. Blood pressure, ECG, oxygen saturation, and core body temperature are obtained and recorded by using a Datascope Passport 2 (Mahwah, NJ). Chimpanzees are maintained in accordance with the *Guide for the Care and Use of Animals*.[15] The facility and its program are fully accredited by AAALAC. No research occurs at the Alamogordo Primate Facility.

In October 2004, a cardiac evaluation was performed including a physical examination during which a sinus rhythm with frequent premature beats was noted. No murmur was detected, and breath sounds were considered normal. Hepatomegaly was noted. Significant clinical laboratory data revealed mild azotemia (BUN, 19 [normal range, 7 to 19]; creatinine, 2.2 [nor-

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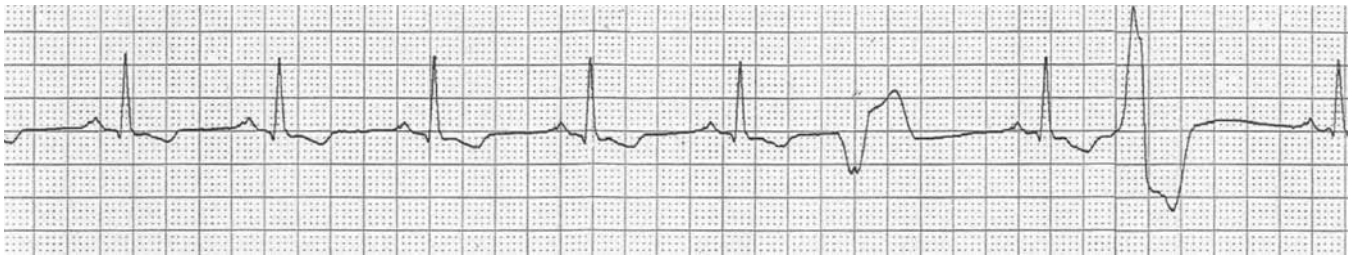

Figure 1. Sinus rhythm with multiform ventricular premature complexes

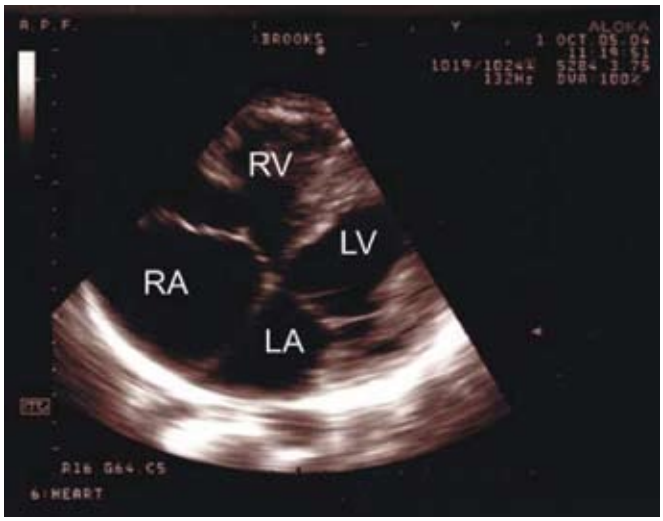

Figure 2. A left-apical 4-chamber echocardiogram demonstrating a severely thickened and dilated right ventricle (RV) and dilated right atrium (RA). LA, left atrium; LV, left ventricle.

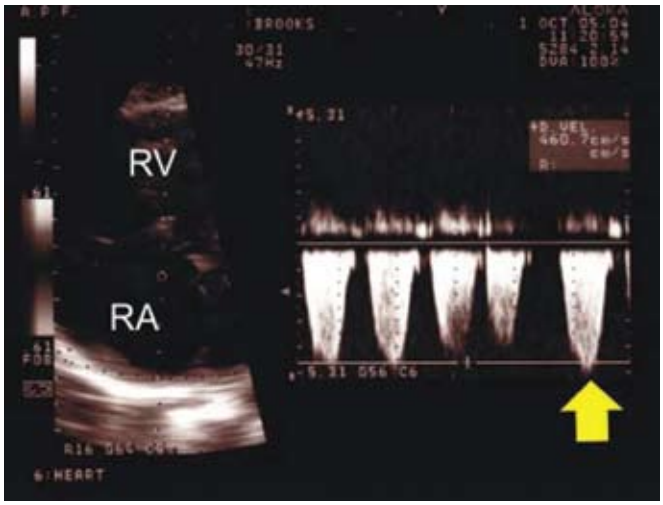

Figure 3. The left side of the image reveals the anatomic site (tricuspid valve) where the Doppler echocardiogram was obtained. Note the elevated tricuspid regurgitation velocity (4.7 m/s), which is consistent with systolic pulmonary arterial hypertension (arrow). RA, right atrium; RV, right ventricle.

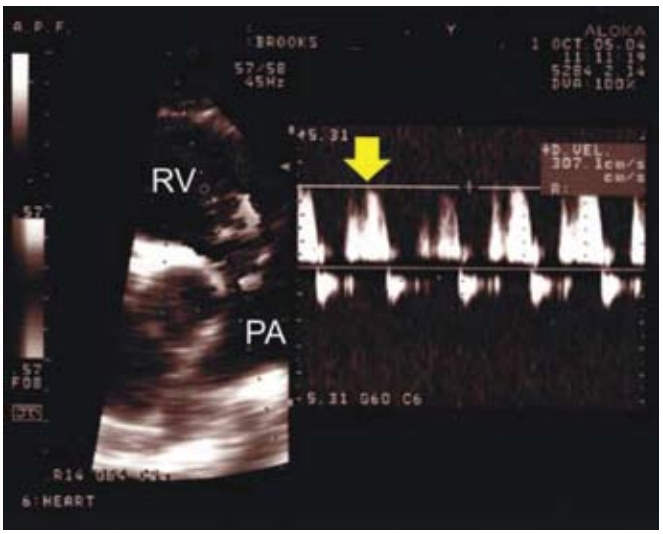

Figure 4. The left side of the image reveals the anatomic site (pulmonic valve) where the Doppler echocardiogram was obtained. Note the elevated pulmonary valve regurgitation velocity (3.07 m/s), which is consistent with diastolic pulmonary arterial hypertension (arrow). PA, pulmonary artery; RV, right ventricle.

mal range, 0.5 to 1.0]). Two-dimensional echocardiography demonstrated severe right atrial and ventricular dilation with concurrent severe right ventricular hypertrophy (Figure 2) and severe pulmonary artery dilation. Mild left ventricular enlargement was present also. High-velocity tricuspid (Figure 3) and pulmonic (Figure 4) valvular regurgitations were present, and pulmonary arterial pressures were estimated by using the modified Bernoulli equation (pressure gradient = $4V^2$, where V is the velocity of the regurgitant jet). Tricuspid regurgitation measured 4.7 m/s and pulmonic regurgitation measured 3.1 m/s, consistent with severely elevated pulmonary arterial pressures of 88 mm Hg (systolic) and 38 mm Hg (diastolic). Idiopathic pulmonary hypertension was diagnosed. A liver biopsy was performed and showed mild hepatic fibrosis and moderate congestion on histopathology. Treatment was initiated with famotidine (0.3 mg/kg once daily) and aspirin (acetylsalicylic acid; 1.2 mg/kg once daily). Treatment with sildenafil (a phosphodiesterase 5 inhibitor) was discussed but not instituted because of lack of experience with the drug in this species.

In April 2005, follow-up physical and cardiovascular examinations were performed. The abdomen was distended due to ascites, and liver congestion was present. A grade 2/5 soft holosystolic murmur was present with a rapid, irregularly, irregular heart rhythm (160 to 180 beats per min), consistent with atrial fibrillation. A complete blood count showed a hematocrit of 56.1% (normal range, 37 to 50) and a blood chemistry revealed an albumin of 2.3 g/dl (normal range, 3.4 to 4.1). The ECG confirmed the presence of atrial fibrillation (Figure 5), and echocardiography revealed similar findings to the previous evaluation as well as evidence of congestive heart failure (mild pericardial and pleural effusions) and reduced systolic function. Pulmonary artery pressures (as estimated by echocardiography) remained severely elevated. In light of the development of atrial fibrillation and right-sided congestive heart failure, medications were initiated to control volume overload and the rapid ventricular response rate.

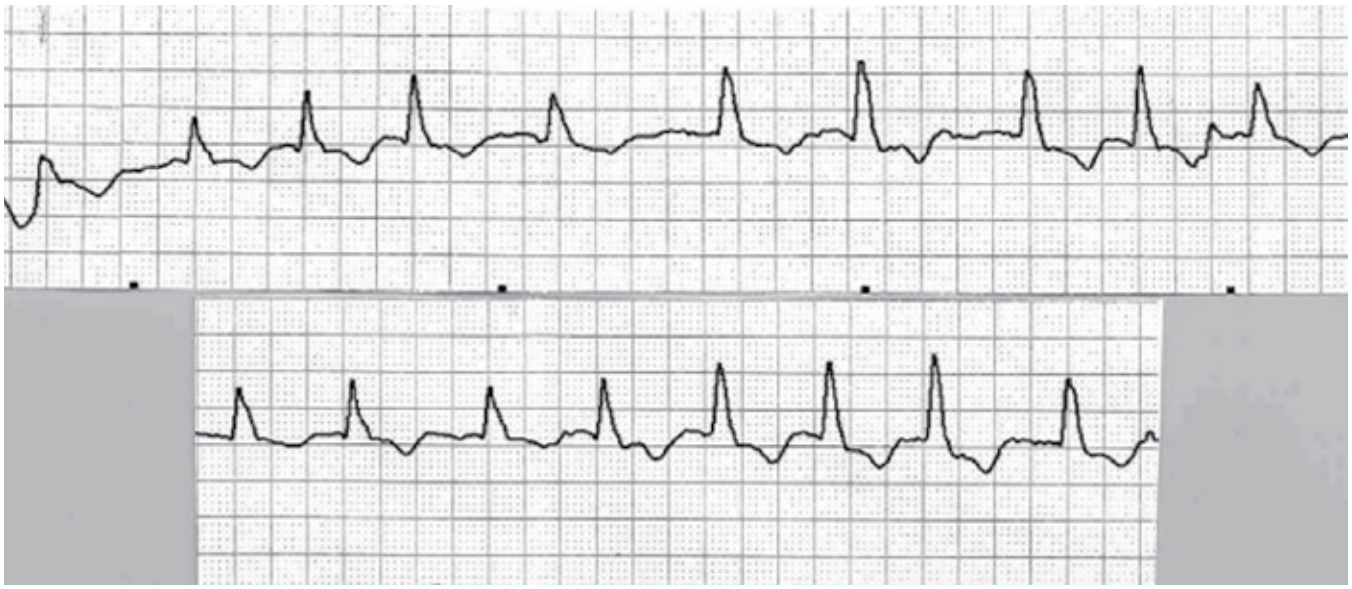

Figure 5. Note the irregularly irregular rhythm and lack of P waves in this ECG, which is consistent with a diagnosis of atrial fibrillation.

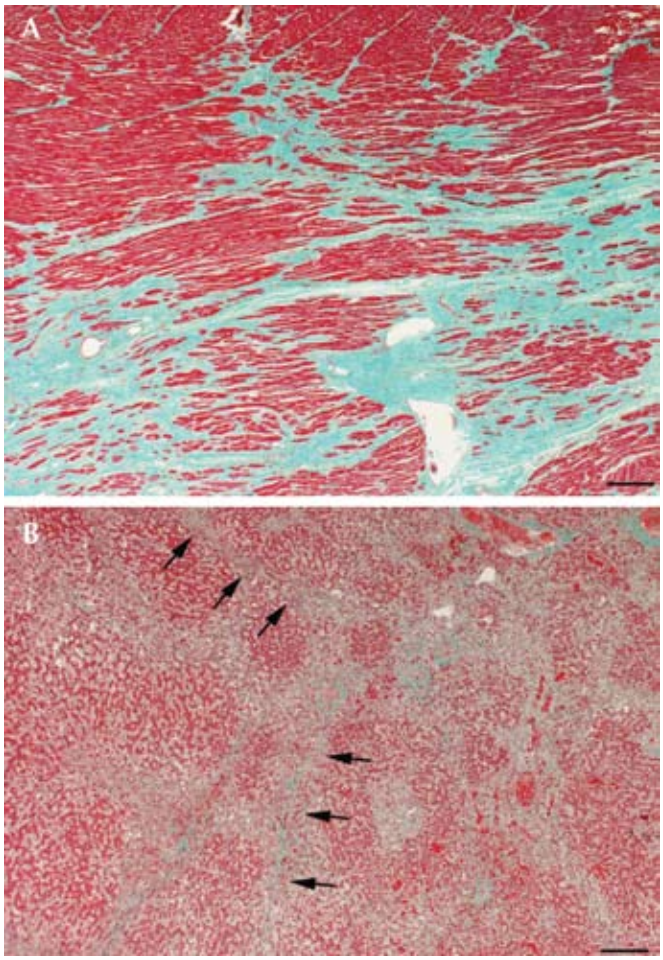

Figure 6. Light microscopic views of representative cardiac and liver changes. (A) Myocardium with moderate amount of fibrous tissue (green) separating and replacing cardiac myocytes (red). Masson trichrome stain; bar, 500 µm. (B) Liver parenchyma demonstrating distortion of normal, regular lobular pattern and linear zones with loss of hepatocytes and 'bridging' fibrosis (arrows). Masson trichrome stain; bar, 250 µm.

The animal was given a loop diuretic (furosemide, 0.7 mg/kg twice daily), digoxin (0.009 mg/kg twice daily for 1 d as a loading dose then 0.0045 mg/kg twice daily), and enalapril (0.3 mg/kg twice daily), and the dose of the acetylsalicylic acid was increased to 3.6 mg/kg once daily. Sildenafil citrate (a PDE5 inhibitor; Viagra, Pfizer, New York, NY; 0.7 mg/kg twice daily) was initiated at this time because of the grave prognosis for survival of this animal.

The animal was placed under intensive care monitoring for 96 h. Mild recumbent coughing, open-mouth breathing with increased respiratory effort, and mild cyanotic mucous membranes (hypoxemia) were noted over the first 24 h; no clinical signs had been noted prior to this point. Within 48 h, he had decreased respiratory effort and increased appetite and fluid intake but positional coughing, open-mouth breathing, and mildly cyanotic membranes were still present. By 72 h, dyspnea and tachypnea had decreased markedly, and the animal had a normal appetite, firm stools, and adequate urine output. He appeared less anxious, with increased interaction and grooming solicitation behavior.

By 96 h, the animal was eupneic, but scrotal edema was noted and believed to be secondary to hypoalbuminemia. Intensive care monitoring was extended for another 48 h, over which time he continued to improve and was placed in a den adjacent to his original social group to slowly reintroduce him without stress. At this time, the only observable abnormality was mild exercise intolerance during brachiating. A low-sodium diet and a 2-wk biscuit count to monitor nutritional intake were initiated. The animal continued to improve, and no adverse effects were noted associated with his treatment regime; however his abdominal distention remained unchanged. He was monitored daily for signs of decompensation.

In June 2005, the ascites and scrotal edema appeared to worsen. Hydrochlorothiazide (0.7 mg twice daily) and spironolactone (0.7 mg twice daily) was initiated help relieve the ascites. By 7 d after treatment, the scrotal edema and ascites both had decreased markedly. Labored breathing, coughing, and exercise intolerance were never noted thereafter, and he was observed to have an active life with normal social interactions.

On October 23, 2005, the animal was observed to be active during the morning enrichment period, but 5 min after

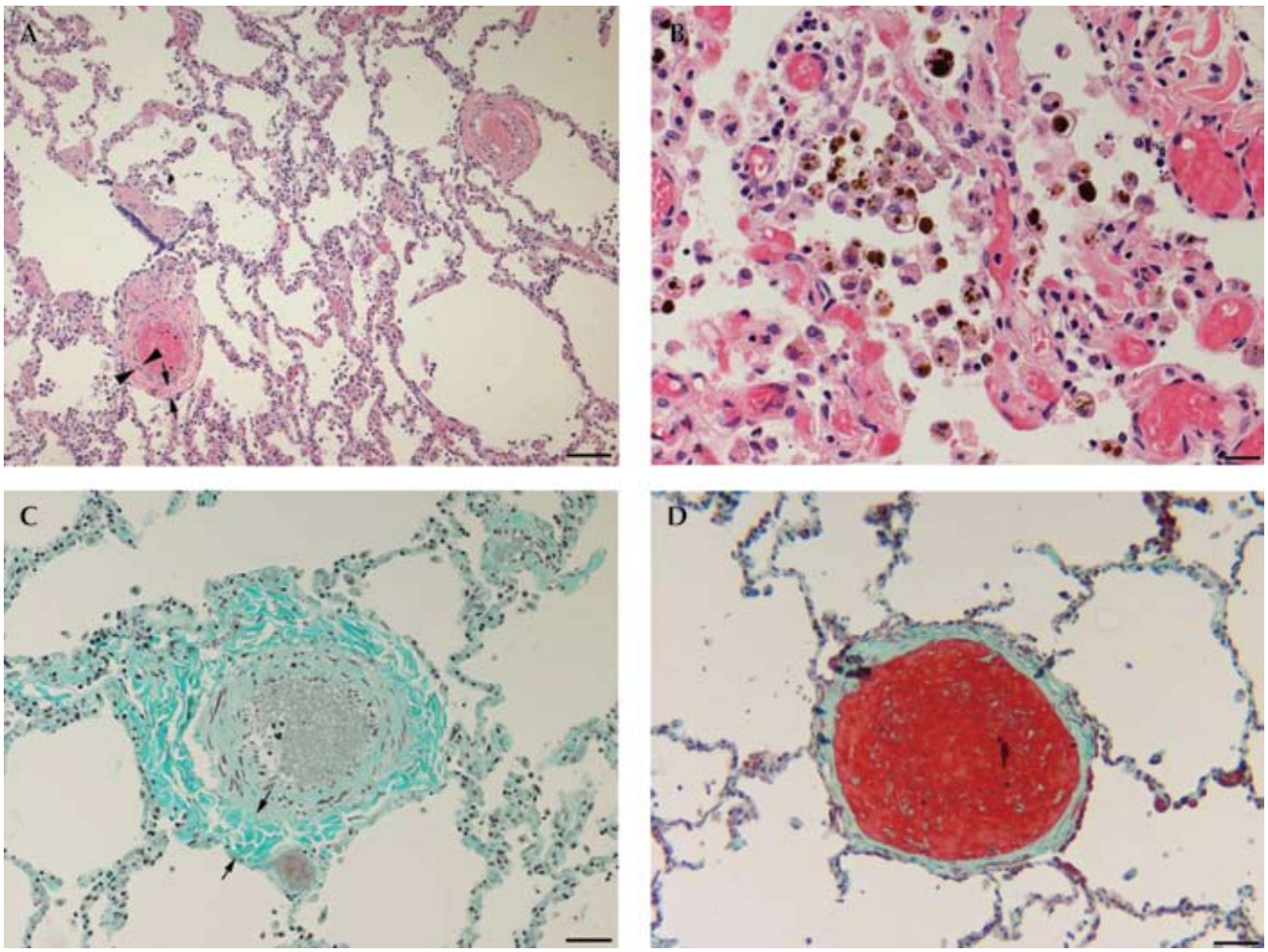

Figure 7. Light microscopic views of representative pulmonary lesions. (A) Small pulmonary arteries with thickened muscular tunic (between arrowheads) and mild to moderate amount of surrounding adventitial fibrous tissue (between small arrows), typical of pulmonary hypertension. Hematoxylin and eosin stain; bar, 100 µm). (B) Aggregate of 'heart failure cells'—alveolar macrophages containing abundant globular brown hemosiderin pigment. Hematoxylin and eosin stain; bar, 20 µm). (C) Collagen-specific staining demonstrating another small pulmonary artery with surrounding mature fibrous connective tissue (bright green tissue between small arrows). Masson trichrome stain; bar, 50 µm. (D) Small pulmonary artery from an age- and gender-matched control. Note the smaller amount of surrounding fibrous tissue (bright green). Masson trichrome stain; bar, 50 µm.

the enrichment was distributed, he was found unconscious. Cardiopulmonary resuscitation and oxygen therapy were initiated promptly. Initial doses of epinephrine (0.5 mg IV) were not effective. Defibrillation was attempted with an automated external defibrillator but was unsuccessful. An ECG revealed no electrical activity, and resuscitation efforts were discontinued.

Gross necropsy revealed extensive adherence of the pericardium to the left crus of the diaphragm. Right ventricular hypertrophy and right atrial dilatation were confirmed. The pulmonary artery was thickened and dilated, and the tricuspid and pulmonic valves appeared grossly normal. The left ventricle appeared subjectively hypertrophied. The liver was enlarged, with rounded edges and areas of fibrosis. Mild ascites and minimal scrotal edema were present. All other organs appeared grossly normal.

Histopathology revealed moderate multifocal interstitial myocardial fibrosis and moderate cardiac myocyte hypertrophy. (Figure 6 A) The lungs contained a mild amount of hemosiderin-laden alveolar macrophages ('heart failure cells'), and mild diffuse fibrosis was present surrounding the small pulmonary arteries. (Figure 7 A to D) The liver contained hemosiderosis with diffuse congestion, bridging fibrosis, and scattered necrotic cells. (Figure 6 B) All other organs appeared histopathologically normal.

Discussion

To our knowledge, this case is the first report of antemortem diagnosis and treatment of pulmonary arterial hypertension and atrial fibrillation in a nonhuman primate. Cardiovascular diseases are a leading cause of morbidity and mortality in captive chimpanzee populations,[9] and echocardiography has been used successfully to diagnose heart disease in chimpanzees.[17] Pulmonary disease occurs in great apes[9,14] but typically is associated with bacterial or viral infections.

Most of the medications used to treat humans with pulmonary hypertension would be impractical to administer to a chimpanzee in group housing. In humans, the most frequently used options are oxygen therapy and injectable prostacyclin. Endothelin receptor antagonists are used also but would be cost-prohibitive in nonhuman primates. Phosphodiesterase 5 inhibitors block the degradation of cGMP, resulting in elevated intracellular cGMP and subsequent relaxation of the pulmonary

vasculature. Sildenifil citrate has proven effective in humans with PAH,[7,11] but its use in great apes had not been reported previously.

Cardiac catheterization by means of a Swan-Ganz catheter is used in human medicine to evaluate the progression of pulmonary hypertension and assist in definitive diagnosis. For all patients in whom pulmonary hypertension still is suspected after chest radiography, ECG, and echocardiography, right-heart cardiac catheterization is recommended to confirm the diagnosis and measure the intracardiac, systemic, and pulmonic pressures and cardiac output.[8] In the present case, the modified Bernoulli equation was used to estimate the pulmonary arterial pressure to avoid the invasive nature of and risks associated with cardiac catheterization.

Sudden cardiac death possibly secondary to right ventricular hypertrophy was the presumed cause of death in this case. The 2 most frequent mechanisms of death in human patients with pulmonary hypertension are right ventricular failure and sudden death.[8]

Congestive heart failure, in this case secondary to pulmonary hypertension, is managed similarly in all species. Diuretics (furosemide, hydochlorothiazide, spironolactone) are used to reduce sodium and water retention; the concurrent use of the 3 diuretic classes is called 'triple diuretic therapy' or 'sequential nephron blockade.' Vasodilators such as angiotensin converting enzyme inhibitors (enalapril) or receptor blockers are used to reduce activity of the renin–angiotensin–aldosterone system.[6] Digoxin is used to slow the ventricular response rate in the presence of atrial fibrillation. This medication also has the benefits of normalizing baroreceptor function (which becomes abnormal in the face of heart failure) and a mild positive inotropic effect.[10] Acetylsalicylic acid reduces platelet aggregation and inflammation and may be beneficial if thromboembolic disease is a factor.

This case demonstrates that treatment of PAH and congestive heart failure in a captive chimpanzee population is not only possible but can improve the quality of life of these animals. Although daily assessment of heart rate monitoring would have resulted in more accurate titration of heart failure medications, monitoring of drug efficacy is much more difficult (if not impossible) in this species compared with humans. However, careful monitoring of behavior changes by a well trained and conscientious technical staff can effectively guide therapy of PAH in chimpanzees.

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