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FIBROSING CARDIOMYOPATHY IN CAPTIVE WESTERN LOWLAND GORILLAS (*GORILLA GORILLA GORILLA*) IN THE UNITED STATES: A RETROSPECTIVE STUDY

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Abstract: Fibrosing cardiomyopathy defined as myocardial replacement fibrosis with atrophy and hypertrophy of cardiac myocytes, absent to mild myocardial inflammation, and no apparent etiology or associated disease condition was identified in 11 captive western lowland gorillas (*Gorilla gorilla gorilla*) in the United States. All 11 were male and ranged from 11 to 37 yr of age ($\bar{x} \pm SD = 26 \pm 8$ yr). In eight cases involving gorillas 16–37 yr of age ($\bar{x} \pm SD = 28 \pm 7$ yr), cardiac scarring was considered fatal. Seven of these eight gorillas died suddenly. Histologically, all eight hearts had multifocal to coalescing, moderate to marked myocardial fibrosis with atrophic and hypertrophied cardiac myocytes. Six gorillas exhibited minimal to mild inflammation, and three had vascular disease. Atherosclerosis was considered contributory in only one case. The deaths of three gorillas with fibrosing cardiomyopathy could not be directly attributed to myocardial fibrosis. Their hearts exhibited similar but less severe myocardial fibrosis than that seen in hearts considered fatally scarred. All three had mild myocardial inflammation, but notable vascular disease was not seen in any gorilla. Fibrosing cardiomyopathy was a significant ($P = 0.007$) cause of sudden death in adult male gorillas in this study. Additional research is necessary to identify the underlying cause(s) of this syndrome and improve the management of the captive gorilla population.

Key words: Western lowland gorilla, *Gorilla gorilla gorilla,* myocardial fibrosis, cardiomyopathy, sudden death.

INTRODUCTION

Chronic heart disease has been reported in captive great apes, but has been presented as either a rare cause of adult mortality or as single case reports.[2,5,7,15,16] In a review of 45 gorilla deaths, there was one report of a 30-yr-old male that died of heart failure and arteriosclerosis.[2] In a review of 226 gorilla deaths, 11 cases of "cardiac arrest" in adult gorillas were reported.[5] Two other cases of myocardial fibrosis in male gorillas, a 13-yr-old and a 24-yr-old, have been reported.[15] Cardiac fibrosis has also been reported in four orangutans and two chimpanzees.[7,16]

The lack of clinical information and detailed gross and histologic descriptions limits our understanding of heart disease in great apes. Increasing knowledge of cardiac diseases will improve our ability to care for great apes in captivity. This report presents a retrospective clinicopathologic investigation of cardiac disease in captive gorillas and identifies possible etiologies.

MATERIALS AND METHODS

Using the 1988 international studbook of the gorilla (*Gorilla gorilla*),[11] 24 western lowland gorillas with cardiac disease that died in captivity in the United States were identified. Both necropsy reports and histologic specimens (tissue sections on glass slides and/or paraffin-embedded tissue) were available for review for nine of these animals. During the course of the investigation, seven more lowland gorillas from U.S. zoological parks that died with evidence of cardiac disease were brought to our attention. Necropsy reports and tissue sections from these animals were available for study. Three gorillas for which necropsy reports and histologic material were available and that died without previously noted cardiac disease

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were included as controls (gorilla nos. 17–19).

The signalments, clinical histories, and gross postmortem findings were derived from necropsy reports. Either the submitted histologic sections or routinely prepared histologic sections of paraffin-embedded tissue stained with hematoxylin and eosin (H&E) were reviewed. In some cases, sections stained with Masson's trichrome stain for collagen, Perl's iron stain, and/or Brown and Brenn and Brown and Hopps Gram stain were also examined.

Fibrosing cardiomyopathy (FCM) was defined as myocardial replacement fibrosis with atrophy and hypertrophy of cardiac myocytes, absent or minimal myocardial inflammation, and no apparent etiology or associated disease. Fibrosing cardiomyopathy was designated mild if $<10\%$ of examined sections of myocardium was replaced by fibrosis, moderate if >10–25% was replaced, and marked if $>25\%$ was replaced.

In addition to histologic evaluation of cardiac disease, the presence or absence of possible cardiac-related microscopic lesions, including pulmonary and hepatic congestion and renal fibrosis, was noted. Other histologic lesions common to more than three gorillas were tabulated in an attempt to identify a significant association with FCM.

Categorical variables (e.g., sudden death, nonsudden death, FCM present or absent, other histologic findings) from all of the gorillas in this study were compared with a Chi-square test (Statview® software, version 4.01). A P-value of ≤ 0.05 was considered significant.

In one gorilla, paired stored sera were tested for evidence of antibodies to encephalomyocarditis virus and coxsackie B virus using standard virus neutralization assays,[8] and hemagglutination inhibition testing[18] was used to determine influenza titers. Additionally, virus isolation was attempted from ultrafrozen sections of spleen, kidney, liver, duodenum, jejunum, and colon and from serum of this gorilla by cocultivation in Vero and L-cells.

RESULTS

Sixteen male and three female gorillas, ranging in age from 9 to 38 yr, that died over a 15-yr period were studied. The results are summarized in Tables 1–3.

Cardiovascular lesions in gorillas with FCM

Fibrosing cardiomyopathy was identified in 11 gorillas (nos. 1–11). All cases of FCM involved male gorillas ranging in age from 11 to 37 yr. Myocardial fibrosis was considered the primary cause of death in eight gorillas (nos. 1–8). Cause of death in three gorillas (nos. 9–11) could not be directly attributed to cardiac fibrosis. Seven gorillas had histories of sudden death, and two others died following anesthesia.

Myocardial fibrosis (Figs. 1, 2) was noted at necropsy in seven of these 11 gorillas, and scarring was specifically described to involve the ventricular septum in three gorillas. In only one gorilla were atherosclerotic plaques of the major vessels reported. Grossly, seven gorillas had pulmonary edema, four had pericardial or pleural effusion, and three had prominently reticulated ("nutmeg") livers.

Histologically, all gorillas with FCM had multifocal to coalescing degenerate, atrophic, absent, and hypertrophied cardiac myocytes surrounded or replaced by dense fibrous connective tissue (Fig. 3). Six hearts had multifocal mild myocarditis, defined as inflammation associated with myocyte necrosis (Fig. 4), and another three had multifocal mild interstitial inflammation. The areas of myocarditis contained a mixture of polymorphonuclear cells, lymphocytes, plasma cells, and histiocytes, whereas the foci of interstitial inflammation contained only lymphocytes, plasma cells, and occasional histiocytes. There were no vascular lesions in six hearts. Mild to moderate intimal thickening of epicardial and myocardial arteries was present in two gorillas, and

Table 1. Clinical parameters of 19 western lowland gorillas.

Gorilla no.	Sex	Age (yr)	Body weight (kg)	Heart weight (g)	HW/BW[a]	Clinical history
1[b]	M	37	173			sudden death
2[b]	M	36	176	820	0.0047	sudden death
3[b]	M	29	185			sudden death
4[b]	M	33	173			sudden death
5[b]	M	16	168	480	0.0029	sudden death
6[b]	M	26	161			sudden death
7[b]	M	24	193			died during recovery from anesthesia
8[b]	M	24	204	785	0.0038	sudden death
9[b]	M	23	214			died during recovery from anesthesia
10[b]	M	25	191			appendicitis and peritonitis
11[b]	M	11	166	586	0.0035	(not available)
12	M	31	144			anorexia, lethargy, regurgitation, diarrhea
13	F	38	69			being treated for cardiac insufficiency
14	F	24	92	700	0.0076	postpartem rupture of dissecting aortic aneurysm
15	F	26	130			died during anesthesia
16	M	9	130	520	0.0040	died during anesthesia
17	M	30	100	449	0.0045	chronic wasting
18	M	18	200			otitis media, disorientation
19	M	14	239	900	0.0037	ataxia, drooping lip, died during anesthesia

[a] Ratio of heart weight/body weight.
[b] Gorillas with fibrosing cardiomyopathy.

mild to moderate arteriosclerosis with occasional atherosclerosis was seen in two others. Another gorilla had diffuse moderate arteriosclerosis with multifocal marked atherosclerosis characterized by up to 80% narrowing of large and small arteries. Mild to moderate systemic arteriosclerosis was also noted microscopically in three of these gorillas.

Cardiovascular lesions in gorillas without FCM

Eight gorillas included in this review (nos. 12–19) died from a variety of causes, including meningitis, euthanasia due to chronic wasting, cerebellar lymphosarcoma, chronic pericarditis, colitis, septicemia, and dissecting aortic aneurysm. In one gorilla, multiple diseases may have contributed to death. These eight gorillas included five 9–31-yr-old males and three 24–38-yr-old females. None of these eight died unexpectedly. Three died during or following anesthesia.

Table 2. Common histologic findings in 19 western lowland gorillas.

Histologic lesion	FCM[a] With	FCM[a] Without	Total
Pulmonary chronic-passive congestion	8/10	5/8	13/18
Hepatic chronic-passive congestion	1/9	2/8	3/17
Hepatic acute-passive congestion	4/9	1/8	5/17
Hepatic hemosiderosis	9/10	7/7	16/17
Splenic hemosiderosis	9/9	4/7	13/16
Renal fibrosis	9/10	6/8	15/18
Cardiac lipofuscinosis	5/11	4/8	9/19
Nodular adrenocortical hyperplasia	5/7	2/3	7/10
Hypospermatogenesis	4/6	3/5	7/11

[a] FCM = fibrosing cardiomyopathy; number of cases with the lesion/number of cases in which the appropriate tissue was submitted. There were no statistically significant differences in noncardiac histologic lesions between animals with and those without FCM.

Table 3. Specific histologic findings[a] in the hearts of 19 western lowland gorillas.

Gorilla no.	No. slides[b]	Fibrosis[c]	Inflammation/ necrosis[d]	Inflammation[e]	Myocyte hypertrophy	Arteriosclerosis
1[f]	10	+++	−	−	+++	+
2[f]	6	+++	+		+++	−
3[f]	13	+++	−	+	+++	+, intimal proliferation
4[f]	8	+++, ventricular septal scar	−	−	+++	++, with marked atherosclerosis
5[f]	2	++	+		++	−
6[f]	14	+++	+		+++	+, intimal proliferation
7[f]	4	+++	+		+++	++, with atherosclerosis
8[f]	3	+++	−	+	++	−
9[f]	7	++, primarily subepicardial	+		+++	−
10[f]	2	+	+		++	−
11[f]	7	+	+		+	−
12	2	−	−	−	−	−
13	1	++, subepicardial	++, lymphoplasmocytic, chronic pericarditis		+	+
14	2	−	−	−	−	−
15	3	++, primarily subepicardial	++, chronic-active, subepicardial myocarditis		+	−
16	12	+, subendocardial	+++, acute myocarditis with cocci		++	+, intimal proliferation
17	5	−	−	−	atrophy	−
18	1	−	−	−	−	+, intimal proliferation
19	3	−	−	−	−	−

[a] + = mild; ++ = moderate; +++ = marked; − = none.
[b] Number of H&E-stained slides of sections of heart available for examination.
[c] Myocardial interstitial fibrosis.
[d] Foci of individual myocardial necrosis with associated inflammation.
[e] Myocardial interstitial inflammation without myocyte necrosis.
[f] Gorillas with fibrosing cardiomyopathy.

Cardiac fibrosis was noted grossly in one of these gorillas and was described as left ventricular subepicardial fibrosis. Necropsy reports stated that two gorillas had pulmonary edema, four had pleural, peritoneal, and/or pericardial effusion, one had a prominently reticulated ("nutmeg") liver, and one had hepatomegaly.

Although multifocal myocardial fibrosis with myocyte atrophy, loss, and hypertrophy was present histologically in four of these gorillas, it was associated with bacterial myocarditis, chronic lymphoplasmocytic pericarditis, chronic-active subepicardial myocarditis, or an aortic aneurysm and therefore was not considered FCM. Except for the cases of bacterial myocarditis, chronic pericarditis, and chronic-active subepicardial myocarditis, none of these gorillas had myocardial inflammation. Although mild

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Figure 1 (top left). Multifocal to coalescing ventricular myocardial fibrosis in a 36-yr-old male western lowland gorilla (no. 2).

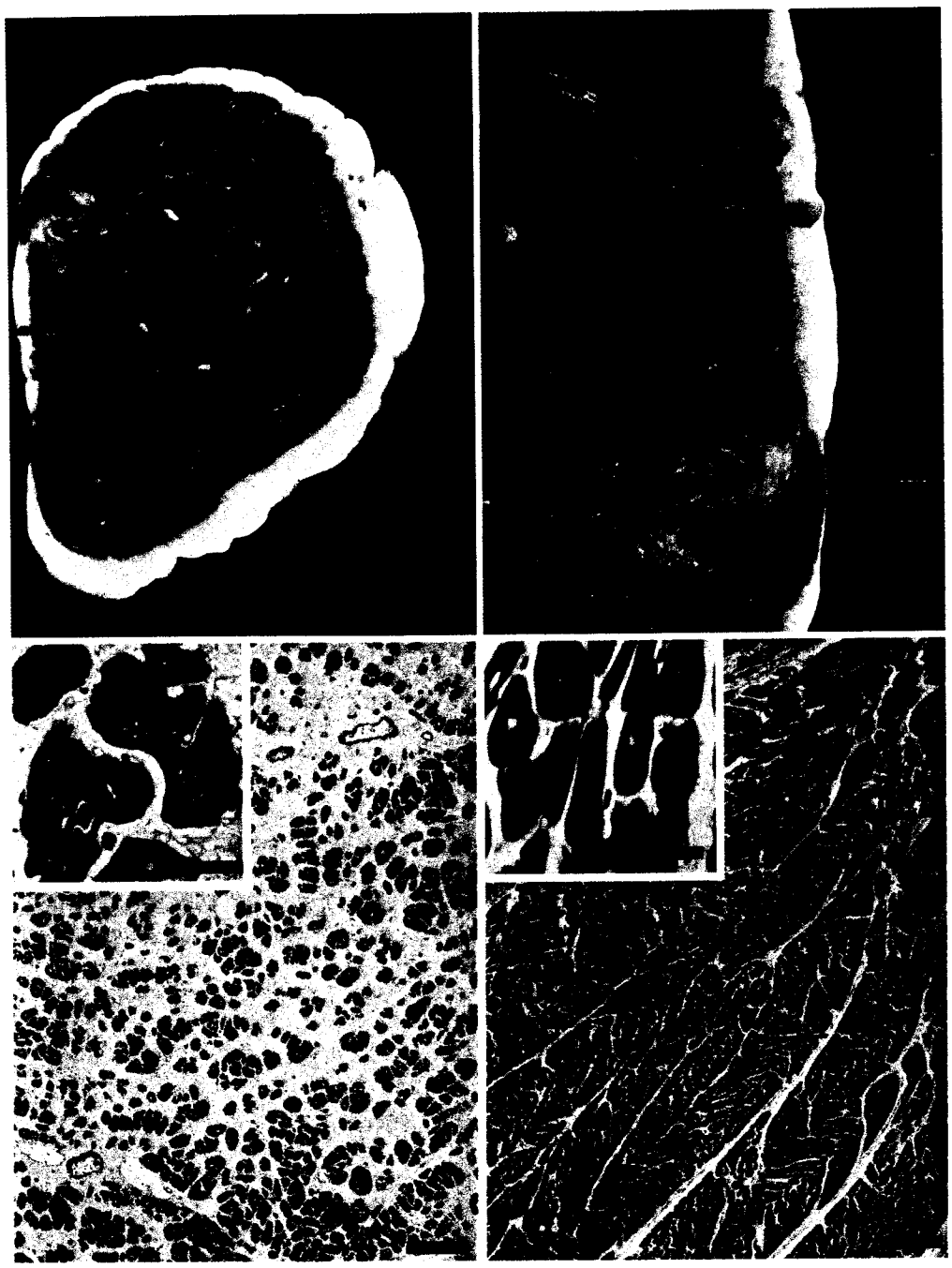

Figure 2 (top right). Higher magnification of the left ventricular free wall of a 36-yr-old male western lowland gorilla (no. 2), showing multifocal to coalescing myocardial scarring.

Figure 3 (bottom left). Cardiac myocytes surrounded and replaced by dense fibrous connective tissue in a 22-yr-old male gorilla (no. 1). Masson's trichrome, bar = 100 μm. *Inset:* Hypertrophy of remaining myocytes with hyperchromatic and pleomorphic nuclei. Masson's trichrome, bar = 10 μm.

Figure 4 (bottom right). Normal myocardium from a 14-yr-old male gorilla, (no. 19). Masson's trichrome, bar = 100 μm. *Inset:* Normal myocardium. Masson's trichrome, bar = 10 μm.

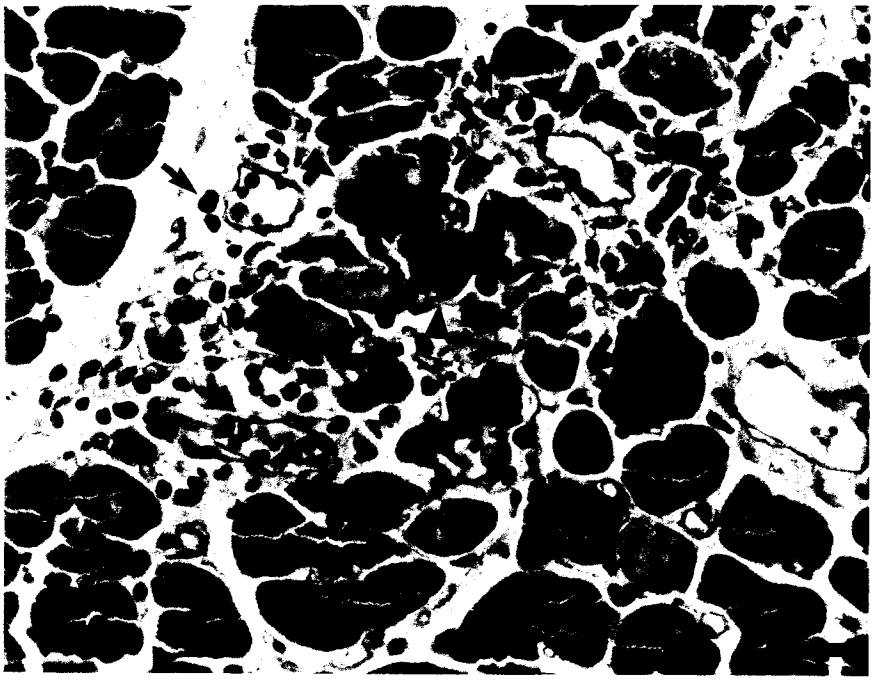

Figure 5. Focal acute myocarditis with myocyte degeneration and necrosis (arrowheads) and associated polymorphonuclear cells (short arrows) in a 16-yr-old male gorilla (no. 5). H&E, bar = 40 μm.

epicardial and myocardial arterial intimal thickening was present in three gorillas, significant cardiac arteriosclerosis and/or atherosclerosis was not seen in any gorilla. The gorilla that was euthanized because of chronic wasting had diffuse atrophy of cardiac myocytes. Three had no histologic lesions of myocardial cells and interstitium (Fig. 5). Microscopic mild systemic arteriosclerosis was noted in the gorilla with chronic pericarditis and the gorilla with the dissecting aneurysm.

Other findings

Although not all organs were available for every gorilla, certain microscopic findings were present in several gorillas, including chronic passive congestion of the lung (13/18 gorillas in which lung was available), acute and chronic passive congestion of the liver (five and three, respectively, of 17 gorillas in which liver was available), hepatic hemosiderosis (16/17 gorillas in which liver was submitted), splenic hemosiderosis (13/16 gorillas in which spleen was submitted), mild to moderate multifocal renal cortical and medullary interstitial fibrosis (15/18 gorillas in which kidney was submitted), cardiac lipofuscinosis (9/19 gorillas in which heart was submitted), nodular adrenocortical hyperplasia (7/10 gorillas in which adrenal gland was submitted), and hypospermatogenesis or aspermatogenesis (7/11 gorillas in which testis was submitted). None of these lesions were significantly correlated with FCM.

The gorilla tested for antibodies to encephalomyocarditis, coxsackie B, and influenza viruses did not show evidence of active infection. No virus was isolated in Vero cell or L-cell cultures.

DISCUSSION

Cardiovascular disease is emerging as an important entity in captive gorillas. Previous gorilla mortality studies have identified death due to cardiovascular disease as being of low prevalence.[2,5,7,15,16] Recently, vascular

disease of gorillas, manifested by dissecting aortic aneurysms, has been highlighted.[1,10] The present study identifies eight gorillas that died from fibrosing cardiomyopathy (FCM) and an additional three gorillas with a less severe form of the condition. Seven of the eight gorilla deaths caused by FCM were sudden, whereas none of the gorillas without FCM experienced sudden death, indicating a significant correlation between sudden death and FCM ($P = 0.007$).

There are several proposed etiologies for cardiomyopathy in great apes, including picornaviruses (coxsackie B and encephalomyocarditis virus) influenza virus, vitamin E/selenium deficiency, hypertension, arteriosclerosis, obesity, stress, and other infectious and toxic agents. Picornaviruses are implicated in >60% of human myocarditis cases.[4] Because the myocardial damage occurs when the amount of detectable virus is greatly reduced or absent, the mechanism of damage is believed to be an induced autoimmunity, although the exact pathogenesis is not known.[6] In experimental models, influenza virus produces a milder disease of shorter duration than does coxsackie B virus. However, influenza is a very common infection, and recurrent infections may lead to cumulative myocardial damage by virus-induced cytolysis, induced autoimmunity, and/or ischemia caused by thrombosed capillaries.[12] Titers to the picornaviruses and/or influenza on paired sera from one gorilla (no. 2) showed no rise in titer, indicating an absence of active infection; however, these findings do not rule out the possibility of one or several past exposures.

Vitamin E deficiency has been suggested as a cause of cardiac fibrosis in gorillas.[15] Two adult male gorillas died unexpectedly with multifocal myocardial fibrosis and previous histories of low plasma alpha tocopherol levels. Vitamin E is an antioxidant and acts synergistically with selenium to protect membranes from high concentrations of lipoperoxidases. Selenium is an integral part of the membrane enzyme glutathione peroxidase, which reduces toxic lipid peroxides to hydroxy acids. Vitamin E and selenium responsive syndromes can cause severe myocardial necrosis in lambs, calves, swine, and horses.[17] Vitamin E deficiency associated cardiomyopathy has been documented in baboons.[13] Vitamin E levels were not evaluated in the present retrospective study.

Obesity, hypercholesterolemia, stress, hypertension, and heredity are additional and often related factors that are associated with cardiovascular disease in human beings.[4] Captive males gorillas have generally lead relatively sedentary lives and are often overweight (FYS and RJM, pers. obs.). Published cholesterol levels for captive gorillas are generally higher than the recommended levels for human beings.[14] Although hypertension is difficult to document in zoo animals and there are no published data on gorilla blood pressures, the presence of systemic arteriosclerosis in five of the 19 gorillas examined suggests some degree of increased vascular resistance. Whether these vascular changes are the cause or the effect of the cardiac lesions remains unknown. Atherosclerosis was considered to be causally related to myocardial scarring in only one gorilla. With severe limitations on importation of wild gorillas, our captive gorilla population has a highly restricted isolated gene pool. If hereditary factors predispose gorillas to conditions such as hypercholesterolemia and hypertension as they do in human beings, individuals with these conditions should be identified and bred accordingly.[4]

The histopathologic findings in the gorilla hearts with fibrosing cardiomyopathy are not specific for a single etiology. All of the possible causes of myocardial degeneration and necrosis can, theoretically, result in cardiac replacement fibrosis. In the few cases in which multifocal, mild, active myocarditis is present, it is unclear if the inflammation is the cause or result of the myocyte necrosis. Chronic-passive congestion of the lungs indicates long-standing left-sided cardiac insufficiency, and chronic-passive congestion of the liver indicates long-standing

right-sided heart failure,[4] but these lesions are not specific for FCM. Acute hepatic congestion is also a nonspecific finding, consistent with terminal cardiac failure.[4]

Hepatic and splenic hemosiderosis has been observed as a common finding in captive nonhuman primates. Although the pathogenesis of this lesion is not known, excessive dietary iron, insufficient dietary tannins or other iron binding substances, and/or high levels of vitamin C in the diet may be involved.[19] Abnormal iron storage can lead to myocardial damage in humans;[4] however, no significant cardiac hemosiderosis was evident in the gorillas of this study.

Multifocal mild renal fibrosis is a common lesion in captive gorillas with and without FCM and is considered of little or no clinical significance. Lipofuscinosis, also known as "wear and tear" pigment, and nodular adrenocortical hyperplasia, which are common findings in older animals,[3,9] also appear to be prevalent in adult gorillas. The youngest gorilla in this study with cardiac lipofuscinosis or adrenocortical hyperplasia was 16-yr-old.

CONCLUSIONS

A review of captive gorillas with cardiac disease reported over a 15-yr period revealed fibrosing cardiomyopathy in 11 gorillas. Fibrosing cardiomyopathy was considered fatal in eight gorillas, and sudden death was the most common clinical feature (7/8 fatal cases). Potential underlying causes of this syndrome include viral infections, nutritional deficiencies, physiologic stress, hypercholesterolemia, sedentary lifestyle, obesity, hypertension, and hereditary factors. Additional study is needed to evaluate these factors to properly manage the captive gorilla population.

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