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Cardiomyopathy and Myocardial Degeneration in Stranded Pygmy (*Kogia breviceps*) and Dwarf (*Kogia sima*) Sperm Whales

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Abstract

Cardiomyopathy (CMP) has been documented as a disease associated with stranded pygmy (*Kogia breviceps*) and dwarf (*Kogia sima*) sperm whales in the United States and Asia. In this study, hearts from 27 pygmy and two dwarf sperm whales stranded in the coastal U.S. Atlantic Ocean and Gulf of Mexico from 1999 to 2006 were analyzed. Gross and microscopic examinations were conducted according to a standardized protocol designed to ensure systematic examination of tissue and data recording. Hearts were weighed and specific measurements made for selected tissues. Fourteen (48.3%) pygmy sperm whales had a microscopic diagnosis of CMP, 12 (41.4%) showed evidence of mild myocardial degeneration (MCD), one (3.4%) had moderate myocarditis and two (6.9%) had no pathological lesions. One dwarf sperm whale had CMP, and the other had mild MCD. The majority of stranded *Kogia* spp. with cardiac lesions came from the southeast Atlantic region (19/27, 70.3%). Cardiomyopathy and MCD lesions were found predominantly among adult whales. An excess of males was found for CMP and MCD (approximately 75% of both groups). The predominant histological lesions found in both disorders were anisokaryosis with karyomegaly and nuclear rowing, followed in frequency by interstitial edema. Cardiac weight, ventricular wall thickness, and valve circumference were compared between pygmy sperm whales with CMP and those with MCD. The largest differences were found for heart weight and intraventricular septum wall thickness, but none of the differences were statistically significant. Further adjustment for sex and body length did not alter the results. In the aggregate, these findings suggest that CMP in *Kogia* spp. is a chronic, progressive condition that represents a continuum from MCD to the more severe forms of the disorder. The etiology of this complex disorder remains unknown.

Key Words: pygmy sperm whale, *Kogia breviceps*, dwarf sperm whale, *Kogia sima*, cardiomyopathy, myocardial degeneration, stranding, U.S. Atlantic Ocean and Gulf of Mexico

Introduction

Cardiomyopathy (CMP) was first described in pygmy (*Kogia breviceps*) and dwarf (*Kogia sima*) sperm whales in 1985 in a study group of 29 beached whales (Bossart et al., 1985). The disease in *Kogia* spp. has been described primarily in whales from the southeastern Atlantic Ocean, but it also occurs in Pacific Ocean whales (Chiu et al., 2003). The etiopathogenesis of the *Kogia* CMP is unknown. Distinct clinical, functional, and pathological patterns of CMP occur in domestic animals and humans, however, and each pattern may be associated with distinct pathogenic mechanisms. While controversies exist with CMP classification schemes, the general clinical, functional, and pathological patterns of CMP are the stress, dilated, hypertrophic, and restrictive forms.

Interest in the etiology and pathogenesis of CMP is ongoing as *Kogia* spp. are the second most common single-stranded cetaceans in the southeastern United States (SEUS) after the bottlenose dolphin (*Tursiops truncatus*). Total annual *Kogia* strandings have ranged from 16 to 69 in the SEUS and from 9 to 40 in Florida (Odell et al., 2004). Annual stranding totals have been highly variable and, at least on the east coast of Florida, may be related to chronic disease and local oceanographic conditions, especially the Gulf Stream (Bossart et al., 1985; Odell et al., 2004). *Kogia* are rarely seen at sea and, despite the relatively high frequency of strandings, very little is known about their biology. In fact, prior to 1966, only one species was recognized (Odell et al., 2004).

The purpose of this study was to further characterize the pathological features of cardiac lesions found in pygmy and dwarf sperm whales using a

newly developed standardized protocol designed to ensure systematic examination of tissue and data recording and to explore potential factors in their etiology.

Materials and Methods

Gross and Microscopic Pathology

The analysis reported here was based on gross and microscopic examination of whole hearts from 27 *K. breviceps* (17 adult males [M], 6 adult females [F], 1 subadult [M], 1 subadult [F], 2 calves [F]) and two *K. sima* (adult [M]) that stranded in the coastal U.S. Atlantic Ocean and Gulf of Mexico between 1999 and 2006 and were submitted to our laboratory for evaluation. A *Kogia* heart dissection manual was developed which describes specific protocols for the collection, fixation, and dissection of heart specimens from *Kogia* spp. (Hensley et al., 2005). Procedures were standardized to ensure systematic gross and microscopic examination of tissue and data recording. *In situ* examination of the heart is detailed in the manual, which also emphasizes the importance of accurately determining the heart weights and specific heart measurements.

Briefly, the formalin-fixed heart was divided into five cross sections of approximately the same width. Cross sections were referred to as Levels 1 through 5, from apex to base, respectively. Heart weights and measurements (right and left ventricular wall thickness at Levels 2 and 4; interventricular septum thickness at Levels 2 and 4; valve circumference [tricuspid, mitral, pulmonary, and aortic]) were determined as described in Hensley et al. (2005). Evaluation included the collection of 12 representative heart sections: septal summit (two blocks), dorsal wall of right ventricle at Level 2, ventral wall of right ventricle at Level 2, dorsal wall of left ventricle at Level 2, ventral wall of left ventricle at Level 2, interventricular septum at Level 2, dorsal wall of right ventricle at Level 4, ventral wall of right ventricle at Level 4, dorsal wall of left ventricle at Level 4, ventral wall of left ventricle at Level 4, and interventricular septum at Level 4. After sectioning, samples were placed into labeled tissue cassettes containing fresh neutral buffered 10% formalin. Tissues were routinely processed, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin for examination by light microscopy. Masson trichrome was used as a special stain to demonstrate the presence of collagen.

Myocardial degeneration (MCD) was diagnosed microscopically as (1) mild, multifocal, or diffuse anisokaryosis with karyomegaly, nuclear rowing, and interstitial edema found in all 12 sections described above; and (2) mild, multifocal, or diffuse eosinophilic homogenization of sarcoplasm and vacuolization, myofiber disarray (architectural disorganization), wavy-attenuated myofibers, and/or loss of cross-striations in six or less sections described above. Fibrosis and inflammation were absent.

A diagnosis of CMP consisted of a suite of microscopic lesions, including multifocal or diffuse: (1) moderate to severe anisokaryosis with karyomegaly and nuclear rowing, (2) moderate to severe interstitial edema, (3) mild to severe eosinophilic homogenization of sarcoplasm and vacuolization, (4) mild to severe myofiber disarray (architectural disorganization), (5) mild to severe wavy-attenuated myofibers, (6) mild to severe loss of cross-striations, and (7) mild to severe fibrosis in 11 or more sections as described above.

Statistical Analyses

Statistical analyses were conducted to determine whether heart weights, wall thicknesses, and valve dimensions differed among *K. breviceps* affected with MCD and CMP. Analyses were limited to *K. breviceps* because the number ($n = 2$) of *K. sima* was inadequate. Further, the morphometrics of these two species would be expected to differ, thus they were not combined. In the first phase of the analysis, all *K. breviceps* with CMP were compared to those with MCD using the *t*-test procedure in *SAS*, Version 9.1 (SAS, Cary, NC). A two-way analysis of variance (ANOVA) was then conducted for heart weight and Level 2 intraventricular septum thickness with diagnosis and sex in the model. Finally, PROC GLM in *SAS* was used to compare heart weight and Level 2 intraventricular septum thickness adjusting for body length in sperm whales with MCD and CMP. An alpha of $p < 0.05$ was considered statistically significant.

Results

The cardiac lesions found in this sample of 29 stranded *Kogia* spp. are summarized in Table 1 along with the geographic region where they occurred. Fourteen (48.3%) whales had a diagnosis of CMP, 12 (41.4%) showed evidence of mild MCD, one (3.4%) had moderate myocarditis, and two (6.9%) had no pathological lesions. Hearts from two *K. sima* were examined: one had evidence of CMP, the other of MCD. Nineteen of 27 (70.3%) *Kogia* spp. with evidence of cardiac pathology came from the southeast Atlantic region that included the east coasts of Florida, Georgia, South Carolina, and North Carolina.

The age and sex distribution of cardiac lesions is shown in Table 2. Lesions occurred predominantly among adult animals. Twenty-five of 27 (92.6%) affected animals were adults and two

Table 1. Cardiac pathology and geographic distribution in 27 pygmy (*Kogia breviceps*) and 2 dwarf (*Kogia sima*) sperm whales

Region	Cardiomyopathy	Myocardial degeneration	Myocarditis	No lesions
SE Atlantic[1]	9	9	1	2
NE Atlantic[2]	1	--	--	--
Gulf of Mexico[3]	4	3	--	--
Totals	**14**	**12**	**1**	**2**

[1]Florida (east coast), Georgia, South Carolina, North Carolina
[2]Maryland, Delaware, New Jersey, New York, Connecticut, Rhode Island, Massachusetts, New Hampshire, Maine
[3]Florida (west coast), Alabama, Mississippi, Louisiana, Texas

Table 2. Cardiac pathology in 27 pygmy (*Kogia breviceps*) and two dwarf[1] (*Kogia sima*) sperm whales by age group and sex

	Cardiomyopathy		Myocardial degeneration		Myocarditis		No lesions	
Age class	Males	Females	Males	Females	Males	Females	Males	Females
Adults	10	3	8	3	1	--	--	--
Subadults	1	--	--	1	--	--	--	--
Calves	--	--	--	--	--	--	--	2
Totals	**11**	**3**	**8**	**4**	**1**	**0**	**0**	**2**

[1]Includes one *K. sima* male with CMP and one *K. sima* male with MCD

(7.4%) were subadults. No pathological findings were observed in the hearts of the two stranded female calves that were examined. Male whales accounted for the majority of myocardial lesions. Twenty of the 27 (74%) affected whales were male; the excess of males occurred for both CMP (78.6% male) and MCD (66.7% male). Lesions of CMP and MCD were further categorized by severity. Eight of the 14 cases of CMP were categorized as severe, five as moderate, and one as mild. All forms of moderate and severe CMP were observed among adult animals. All cases of MCD were classified as mild.

Among *Kogia* with CMP, anisokaryosis with karyomegaly and nuclear rowing was the most common histological finding (Figures 1, 2 & 3) and was observed in 133 of the 168 (79.2%) tissue blocks examined in the 14 affected whales. In descending frequency, the next most common histological lesions were interstitial edema (61.3%), myofiber disarray (26.2%) (Figure 4), loss of cross-striations (20.2%) (Figure 1), eosinophilic homogenization of sarcoplasm (20.2%), and interstitial edema with fibrosis (17.3%) (Figures 3 & 5). In most cases, the anatomic distribution of each lesion was relatively similar across the 12 sampling sites. There were some exceptions to this observation, however. For example, the frequency of detection of anisokaryosis varied between interventricular septal sites. The distribution of histopathological lesions of CMP in *Kogia* spp. was analyzed according to their anatomical location; the results are shown in Appendix 1.

Anisokaryosis with karyomegaly and nuclear rowing was also the predominant histological lesion in the 12 *Kogia* with MCD. This lesion was observed in 106 of the 144 (73.6%) tissue blocks examined. The frequency of other histological lesions generally followed the pattern observed in whales with CMP, with interstitial edema (37.5%) the next most commonly found lesion. The frequency of myofiber disarray (5.6%), loss of cross-striations (6.9%), eosinophilic homogenization of sarcoplasm (1.4%), and interstitial edema with fibrosis (2.1%) were substantially lower than those observed in cases of CMP. As was found for CMP, the anatomical distribution of each lesion of MCD was relatively similar across the 12 sampling sites. The distribution of MCD lesions by anatomical location is shown in Appendix 2.

A single case of moderate, multifocal chronic myocarditis without concurrent CMP or MCD was also present. The predominant inflammatory cell type was mature lymphocytes. No infectious agents were observed, and the etiology was not determined.

No statistically significant differences were found between pygmy sperm whales with CMP and those with MCD for any of the 11 parameters tested. Differences in heart weight; right and left

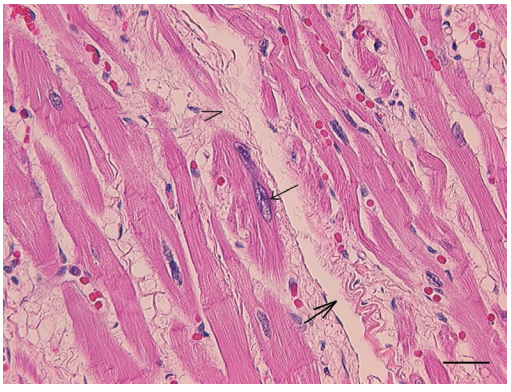

Figure 1. Photomicrograph of heart of a pygmy sperm whale with cardiomyopathy; note the anisokaryosis with karyomegaly (small arrow), loss of cross-striations (arrowhead), and interstitial edema (large arrow). H&E stain; bar = 80 microns.

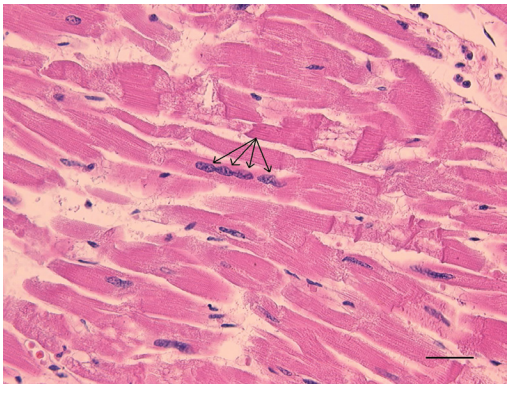

Figure 2. Photomicrograph of heart of a pygmy sperm whale with cardiomyopathy; note the nuclear rowing of cardiomyocytes (arrows). H&E stain; bar = 80 microns.

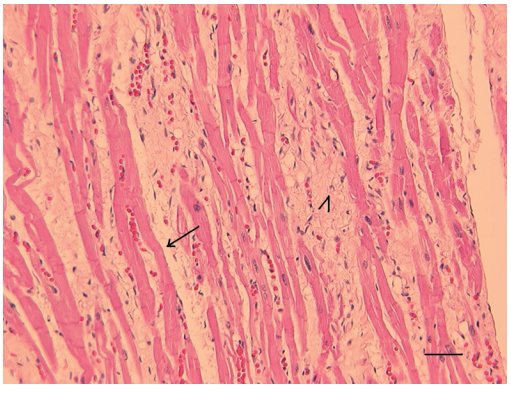

Figure 3. Photomicrograph of heart of a pygmy sperm whale with cardiomyopathy; note the interstitial edema (arrow) and presumptive fibrosis (arrowhead). H&E stain; bar = 150 microns.

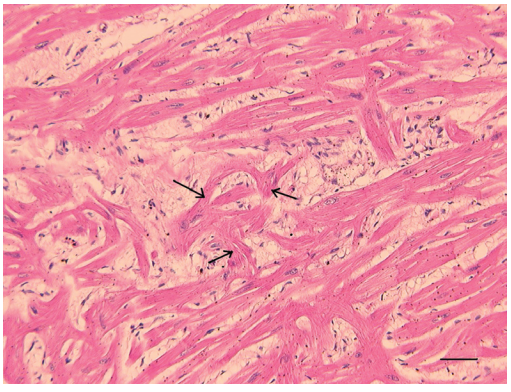

Figure 4. Photomicrograph of heart of a pygmy sperm whale with cardiomyopathy; note the myofiber disarray and architectural disorganization of cardiomyocytes (arrows). H&E stain; bar = 150 microns.

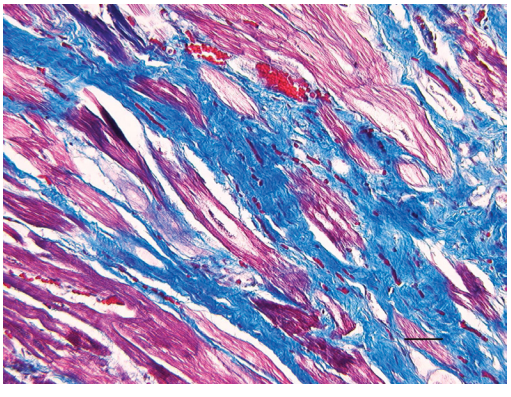

Figure 5. Photomicrograph of heart of a pygmy sperm whale with cardiomyopathy; note the diffuse thickened blue fibrillar deposits of collagen. Masson trichrome stain; bar = 120 microns.

ventricular wall thickness at two levels; intraventricular septum thickness at two levels; and circumference of the aortic, pulmonary, mitral, and tricuspid valves were evaluated. The largest differences were found for heart weight and intraventricular septum wall thickness, but none were statistically significant (Table 3). An ANOVA with sex in the model was run to determine whether sex could be acting as a confounder since males would be expected to be larger and were selectively affected. The mean heart weight for *K. breviceps* with CMP was greater than that for MCD for both males and females, but the differences were not statistically significant ($p = 0.14$) (Table 4). Finally, body length was used as a surrogate for body weight to adjust the heart weight data in PROC GLM. The adjusted least square mean heart weight for *K. breviceps* with CMP (1.63 kg)

Table 3. Heart weight, wall thickness, and valve circumference in *Kogia breviceps* with cardiomyopathy and myocardial degeneration

Cardiac parameter	Cardiomyopathy		Myocardial degeneration		P value
	Mean	SD	Mean	SD	
Heart weight (kg)	1.7	0.27	1.4	0.53	0.12
L2 RV wall (cm)	0.5	0.18	0.6	0.25	0.92
L2 LV wall (cm)	1.0	0.47	1.1	0.61	0.54
L2 IV wall (cm)	1.7	0.68	1.3	0.44	0.20
L4 RV wall (cm)	0.7	0.28	0.9	0.60	0.45
L4 LV wall (cm)	1.2	0.58	1.2	0.49	0.86
L4 IV septum (cm)	2.1	0.80	1.8	0.45	0.37
Pulmonary valve (cm)	12.6	1.84	11.8	2.71	0.47
Aortic valve (cm)	11.9	2.34	10.8	2.31	0.38
Tricuspid valve (cm)	19.6	5.24	16.9	2.63	0.26
Mitral valve (cm)	16.3	3.72	14.5	3.28	0.33

Table 4. Heart weight by sex in *Kogia breviceps* with cardiomyopathy and myocardial degeneration

Sex	Cardiomyopathy			Myocardial degeneration		
	Number	Mean weight (kg)	SD	Number	Mean weight (kg)	SD
Males	9	1.7	0.26	8	1.4	0.50
Females	2	1.8	0.42	3	1.4	0.71
Totals	11			11		

*p = 0.14

was greater than that for MCD (1.52 kg), but the difference was not statistically significant (data not shown).

Discussion

The pathological data presented in this report suggest that CMP is a common lesion in *Kogia* spp. that stranded in the coastal waters of the U.S. Atlantic and Gulf of Mexico from 1999 to 2006. These data support and extend a past report of *Kogia* spp. that stranded in the same geographic region from 1980 to 1984 (Bossart et al., 1985). All of the whales in the present study represent single strandings. The consistency, extent, and severity of the pathological lesions suggest that many of these whales were in a state of myocardial decompensation at the time of stranding. Furthermore, this study provides new evidence indicating that *Kogia* CMP is a chronic progressive condition rather that an acute terminal event. Specifically, the similarity in type and distribution of pathological lesions of CMP and MCD implies a continuum of the same process. Thus, MCD may precede and lead to the development of CMP as the whales age. The apparent progressive nature of CMP ultimately would result in a debilitating condition in adults; and the beaching event of the ailing whales would be dependent on the active movement (or lack of purposeful directional movement) and prevailing environmental conditions such as ocean steering currents and weather conditions. The general trend of greater heart weights in *K. breviceps* with CMP compared to those with MCD supports the hypothesis that the disorder is a progressive condition since heart weight may be increased with CMP in other species (see below). It is important to note that none of the heart weight, wall thickness, or valve circumference differences were statistically significant and that the statistical analyses compared whales with CMP to whales with MCD; an unaffected comparison group was not available.

In terrestrial mammals and humans, the general types of CMP include stress, hypertrophic, dilated (congestive), and restrictive forms. The myocardial lesions of the stress, dilated, and hypertrophic CMP types described in other species were observed in the present study.

The stress form represents an acute process mediated by catecholamines, which may lead to sudden death in humans and animals, usually without a history of pre-existing heart disease (Cebilin & Hirsch, 1980; Liu et al., 1982). Elevated endogenous catecholamines produce a distinctive focal hypercontraction and lysis of contractile filaments

in small groups of cardiomyocytes that is termed "contraction band necrosis" (Turnbull & Cowan, 1998). Contraction band necrosis, including loss of cross-striations, interstitial edema, myofiber cytoplasmic hypereosinophilia, and wavy fibers, have been reported previously in the *Kogia* CMP and in other stranded cetaceans (Bossart et al., 1985; Turnbull & Cowan, 1998). Additionally, a more chronic stress hormone component involving cortisol has recently been described in dogs with dilated CMP (Tidholm et al., 2005).

Hypertrophic CMP is well characterized in humans and domestic animals (Liu et al., 1993, 1994; Maron, 1997). The demonstration of specific genetic abnormalities in cardiac energy metabolism or structural and contractile proteins results in approximately half the human cases of hypertrophic CMP (Hughes, 2004). The diagnosis of this form is based on macroscopic enlargement of the heart usually supported by microscopic lesions consisting of myofiber disarray (architectural disorganization). In *Kogia*, heart enlargement is difficult to assess because normal heart weights have not been determined; however, the microscopic lesion of myofiber disarray associated with hypertrophic CMP in other species was seen in 26% of *Kogia* with CMP.

In about half of the human patients with hypertrophic CMP, the disease is familial and is one of the most common causes of a sudden, unexplained death in young male athletes (Schoen, 1999). The preponderance of male whales with myocardial pathology in the current study was a new and interesting finding. In contrast, an earlier study did not find an unusual sex distribution (Bossart et al., 1985). The significance of the excess of CMP among male *Kogia* is unknown but may suggest a sex-linked genetic etiology.

Dilated CMP differs from the hypertrophic form in that the capacity of the ventricle(s) is actually increased, which can impart a "globular" appearance to the heart. In the fresh unfixed heart, the ventricle(s) may feel flabby. Dilated CMP in humans has varied etiologies that may involve complex mechanisms, including postinfectious, autoimmune, and idiopathic factors (Richardson et al., 1996). Dilated CMP also has been associated with L-carnitine and taurine deficiencies in humans, rodents, and domestic animals (Levitan et al., 1987; Keene, 1991; Fascetti et al., 2003; Zaugg et al., 2003). Dilated CMP was recently reported in southern California sea otters (*Enhydra lutris nereis*) and postulated to be associated with domoic acid toxicosis and depletion of myocardial L-carnitine (Kreuder et al., 2005).

The first report of CMP in *Kogia* was a dilated form, which included a grossly dilated flabby right ventricle, generalized myocardial pallor, and chronic passive congestion of the liver (Bossart et al., 1985). The etiology of this case of dilated CMP could not be determined, but nutritional etiologies, including a thiamine deficiency, were postulated. Thiamine deficiency has been reported in captive marine mammals, and myocardial lesions consistent with thiamine deficiency were seen in captive sea lions fed a diet presumably containing high concentrations of thiaminase (Rigdon & Drager, 1955; Worthy, 2001). In this study, it was difficult to assess the occurrence of gross myocardial changes of dilated CMP as all of the examined hearts had already been fixed, thus distorting normal gross morphology. Previously described microscopic heart lesions of the dilated form were found, however, and these consisted of cardiomyocyte degeneration, loss of cross-striations, interstitial edema, and fibrosis (Bossart et al., 1985).

Although each form of CMP is fundamentally different, they are not necessarily mutually exclusive in a given case. Moreover, transitions from one type to another may occur in humans, reflecting chronicity and/or severity of the basic disease process (Hughes & McKenna, 2005). Specifically, hypertrophic CMP may progress to a dilated phase in human patients and resemble dilated CMP (Maron, 2002). Therefore, it appears that the *Kogia* CMP may be best defined as a "mixed form," having microscopic components of all three types. Lesions seen uniformly in all sections included eosinophilic homogenization of sarcoplasm, loss of cross-striations, interstitial edema and fibrosis, anisokaryosis with karyomegaly, myofiber disarray (architectural disorganization), and wavy-attenuated myofibers. Thus, the etiology of CMP in *Kogia* is likely complex and multifactorial. Etiologic components may include metabolic factors, such as excessive repeated sublethal episodes of catecholamine release (repeated acute "stress" reactions) and endogenous glucocorticoid release (chronic "stress" response); nutritional deficiencies; and postinfectious, genetic, and toxic factors (e.g., biotoxins). Further studies may help confirm these hypotheses.

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Appendix 1. Distribution of histopathological lesions of cardiomyopathy by anatomic site (n = 14)

Histological lesion	SS-1	SS-2	DRV-2	VRV-2	DLV-2	VLV-2	IV-2	DRV-4	VRV-4	DLV-4	VLV-4	IV-4	Total
Anisokaryosis with karyomegaly and nuclear rowing	9 (64%)	9 (64%)	11 (79%)	12 (86%)	12 (86%)	11 (79%)	7 (50%)	13 (93%)	12 (86%)	12 (86%)	11 (79%)	14 (100%)	133 (79.20%)
Interstitial edema	8 (57%)	5 (36%)	9 (64%)	9 (64%)	8 (57%)	9 (64%)	6 (43%)	10 (71%)	9 (64%)	9 (64%)	9 (64%)	12 (86%)	103 (61.30%)
Myofiber disarray (architectural disorganization)	1 (7%)	2 (14%)	4 (29%)	4 (29%)	4 (29%)	5 (36%)	3 (21%)	3 (21%)	3 (21%)	3 (21%)	5 (36%)	7 (50%)	44 (26.20%)
Loss of cross-striations	1 (7%)	2 (14%)	1 (7%)	3 (21%)	5 (36%)	4 (29%)	1 (7%)	2 (14%)	2 (14%)	5 (36%)	4 (29%)	4 (29%)	34 (20.20%)
Myofiber cytoplasmic hypereosinophilia	2 (14%)	2 (14%)	1 (7%)	2 (14%)	2 (14%)	5 (36%)	2 (14%)	3 (21%)	4 (29%)	4 (29%)	4 (29%)	3 (21%)	34 (20.20%)
Interstitial edema and fibrosis	0 (0%)	5 (36%)	2 (14%)	1 (7%)	4 (29%)	3 (21%)	1 (7%)	3 (21%)	2 (14%)	3 (21%)	3 (21%)	2 (14%)	29 (17.30%)
Wavy-attenuated myofibers	0 (0%)	1 (7%)	1 (7%)	2 (14%)	1 (7%)	1 (7%)	2 (14%)	1 (7%)	2 (14%)	2 (14%)	2 (14%)	2 (14%)	17 (10.10%)

SS-1 = Septum summit to the right of the midline
SS-2 = Septum summit to the left of the midline
DRV-2 = Dorsal right ventricle at Level 2
VRV-2 = Ventral right ventricle at Level 2
DLV-2 = Dorsal left ventricle at Level 2
VLV-2 = Ventral left ventricle at Level 2
IV-2 = Interventricular septum at Level 2
DRV-4 = Dorsal right ventricle at Level 4
VRV-4 = Ventral right ventricle at Level 4
DLV-4 = Dorsal left ventricle at Level 4
VLV-4 = Ventral left ventricle at Level 4
IV-4 = Interventricular septum at Level 4

Appendix 2. Distribution of histopathological lesions of myocardial degeneration by anatomical site (n = 12)

Histological lesion	SS-1	SS-2	DRV-2	VRV-2	DLV-2	VLV-2	IV-2	DRV-4	VRV-4	DLV-4	VLV-4	IV-4	Total
Anisokaryosis with karyomegaly and nuclear rowing	9 (75%)	9 (75%)	6 (50%)	7 (58%)	11 (92%)	11 (92%)	10 (83%)	5 (42%)	8 (67%)	9 (75%)	9 (75%)	12 (100%)	106 (73.6%)
Interstitial edema	4 (33%)	3 (25%)	4 (33%)	4 (33%)	5 (42%)	6 (50%)	5 (42%)	2 (17%)	2 (17%)	5 (42%)	6 (50%)	8 (67%)	54 (37.5%)
Myofiber disarray (architectural disorganization)	1 (8%)	0 (0%)	2 (17%)	0 (0%)	1 (8%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)	0 (0%)	8 (5.60%)
Loss of cross-striations	1 (8%)	1 (8%)	0 (0%)	0 (0%)	1 (8%)	2 (17%)	2 (17%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	2 (17%)	10 (6.9%)
Myofiber cytoplasmic hypereosinophilia	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	2 (1.40%)
Interstitial edema and fibrosis	1 (8%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2.10%)
Wavy-attenuated myofibers	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (0.7%)

SS-1 = Septum summit to the right of the midline
SS-2 = Septum summit to the left of the midline
DRV-2 = Dorsal right ventricle at Level 2
VRV-2 = Ventral right ventricle at Level 2
DLV-2 = Dorsal left ventricle at Level 2
VLV-2 = Ventral left ventricle at Level 2
IV-2 = Interventricular septum at Level 2
DRV-4 = Dorsal right ventricle at Level 4
VRV-4 = Ventral right ventricle at Level 4
DLV-4 = Dorsal left ventricle at Level 4
VLV-4 = Ventral left ventricle at Level 4
IV-4 = Interventricular septum at Level 4