Spontaneously Occurring Arrhythmogenic Right Ventricular Cardiomyopathy in the Domestic Cat
A New Animal Model Similar to the Human Disease

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Background—Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary myocardial disease of incompletely resolved pathogenesis and is a largely unappreciated cause of sudden death in the young.

Methods and Results—Clinical features of 12 domestic cats with ARVC (7 male; 1 to 20 years old, mean 7.3 ± 5.2 years) were right-sided congestive heart failure (n=8), supraventricular tachyarrhythmias (n=5), ventricular tachycardia (n=3), polymorphic ventricular arrhythmias (n=6), and right bundle-branch block (n=5). ARVC was suspected in all 8 cats examined with echocardiography by marked enlargement of the right ventricle (RV) and right atrium and tricuspid regurgitation. Eight died of cardiovascular disease and 4 died of noncardiac conditions. At autopsy, hearts of ARVC cats were characterized grossly by moderate-to-severe RV cavity enlargement and wall thinning (n=12) and apical aneurysm formation (n=6). Histology demonstrated pronounced RV lesions in all 12 ARVC cats, including marked myocytic injury (myocyte death and atrophy) and repair (fibrous and/or fatty replacement). Injury and repair were also evident in the left ventricle (LV) in 10 cats, and 2 had involvement of both atria. Myocarditis was present in 10 of the 12 ARVC cats. Apoptosis was detected in 9 ARVC cats (mean apoptotic index, 28 ± 18% RV, 21 ± 19% LV, and 17 ± 15% ventricular septum) but not in controls.

Conclusions—In the common domestic cat, we identified a clinically relevant cardiomyopathy that closely mimics ARVC in humans. This unique feline model of human disease will be relevant to defining pathogenesis and investigating mechanisms responsible for disease progression in ARVC. (Circulation. 2000;102:1863-1870.)

Key Words: arrhythmia ▪ cardiomyopathy ▪ myocarditis ▪ apoptosis ▪ heart diseases

A rrhythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon but important primary myocardial disease of incompletely resolved pathogenesis. It is responsible for substantial cardiovascular morbidity in humans1–6 and is a largely unappreciated cause of sudden death in the young.7,8 Discerning the basic mechanisms responsible for progressive atrophy of the right ventricular (RV) myocardium with fibrous and/or fatty replacement in ARVC has been impaired by the absence of an appropriate animal model. We and others have reported that the domestic cat harbors primary myocardial diseases similar to those in humans, particularly hypertrophic cardiomyopathy.9–12 Thus, we document a naturally occurring cardiomyopathy in domestic cats that closely resembles ARVC in humans.

Methods

Selection of Animals
Between June 1995 and June 1998, pathology archives of The Animal Medical Center (Caspary Research Institute and Bobst Hospital) were reviewed for cases in which death appeared to be due to congestive heart failure (CHF) of RV origin; 26 cats were identified. Fourteen were excluded for congenital or acquired cardiovascular anomalies; the remaining 12 hearts were suspected of ARVC on the basis of marked RV and atrial (RA) enlargement with grossly identifiable wall thinning and were selected for detailed gross and histological examination.

These 12 study animals (2.9 to 7.3 kg, mean 4.8 ± 1.5 kg) were 1 to 20 years old (mean 7.3 ± 5.2 years). Seven were male. Breeds included domestic shorthair (n=8), Burmese (n=2), and Burman (n=2). Selected as normal controls were 6 other domestic shorthair cats (2.9 to 5.9 kg, mean 4.5 ± 1.1 kg) that died of trauma without evidence of cardiovascular disease. These were 2 to 11 years old (mean 6.5 ± 3.4 years); 4 were male. Control cats did not differ significantly from ARVC cats with regard to age, sex, or body weight.

Echocardiographic Methods
Echocardiograms were made with a commercially available Vingmed CFD 775 instrument. 2D and M-mode studies were completed with a 7.5-MHz transducer and Doppler echocardiographic recordings with a 5-MHz transducer. Echocardiographic images were
recorded at 100 mm/s on ¾-in format videotape with the subjects unsedated and manually restrained by a technician.

Echocardiographic examination was performed with a technique we previously described10,13 to achieve, as closely as possible, the standard cross-sectional planes described in humans. M-mode echocardiograms were derived from 2D images under direct anatomic visualization. Measurements were made from the M-mode echocardiogram (averaging 3 to 5 consecutive cycles) and compared with normal values previously obtained in healthy cats without cardiovascular disease.10,14 Valvular regurgitation was assessed with color-flow Doppler echocardiography.

Pathological Methods
Complete necropsy examinations were performed in all 12 cats. Transillumination was used to aid in detection of focal RV wall thinning.1 Hearts were fixed in 10% phosphate-buffered formalin.

We used a semiquantitative scoring system to describe cardiac chamber dilatation: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.1 A 4-chamber long-axis or short-axis cut of the entire heart was embedded in paraffin for histological analysis. Transmural tissue blocks were taken perpendicular to the long axis of the RV wall, left ventricular (LV) free wall, and ventricular septum. Blocks were also taken from RA and left atrial (LA) walls. Tissue sections were cut 5 μm thick and stained with hematoxylin and eosin and Heidenhain (azan) trichrome stains. Wall thicknesses were measured from endocardium to epicardium (excluding epicardial fat) from tissue sections with the aid of light microscopy and a micrometer. In left and right atria, ventricular septum, and LV free wall, measurements of wall thickness were made at 3 sites, and an average thickness was calculated; RV wall thickness was measured in the 3 regions of the “triangle of dysplasia”15 (ie, inflow, outflow, and apex), and these measurements were averaged.

Immunohistochemical investigation characterizing inflammatory infiltrates with regard to cell types used antibodies against endothelial cells (factor VIII–related antigen antibody, polyclonal, from Dako), T lymphocytes (CD3 polyclonal antibody, from Dako, 1:50),15 and B lymphocytes (Cd79a antibody HM57, from Immunotech, 1:50)16 according to the avidin-biotin-peroxidase complex method (Vector).

To establish whether apoptosis is present in feline ARVC or controls, myocardium was examined by terminal deoxynucleotidyl transferase–mediated dUTP-biotin nick end-labeling method (TUNEL). Sections were processed in accordance with Gavrieli’s method.17 To determine the apoptotic index, single tissue sections were taken from RV and LV walls and ventricular septum (avoiding tissue edges). The index was calculated as the number of positive myocytes divided by the total number of myocytes, with that value multiplied by 100.18

Statistical Analysis
Data are expressed as mean ± SD. Differences between continuous variables were analyzed with unpaired Student’s t test or Mann-Whitney rank sum test; differences between proportions were assessed with Fisher’s exact test. A value of P < 0.05 was regarded as significant.

Results
Clinical Presentation
Eight of the 12 cats presented a clinical profile of right-sided CHF with tachypnea, jugular vein distention, abdominal effusion, or hepatosplenomegaly; syncope occurred in 1 cat. Eight cats had soft, pansystolic heart murmurs along the right sternal border consistent with tricuspid regurgitation. The 4 remaining cats presented with lethargy and anorexia but had no objective evidence of CHF.

Radiography
Thoracic radiographs (lateral and ventrodorsal projections) were obtained in all cats. Enlargement of the cardiac silhouette compatible with RA and RV dilatation were judged to be present in all 12 animals. LA enlargement was also observed in 6 cats. Eight of the 12 cats had additional radiographic changes compatible with right-sided CHF, including pleural effusion (n = 8), ascites (n = 4), pericardial effusion (n = 3), and inferior vena caval dilatation (n = 2).

Electrocardiography
ECGs were obtained in 8 cats within 48 hours of death. A variety of arrhythmias were recorded (Figure 1), including ventricular tachycardia (n = 3), atrial fibrillation (n = 4), supraventricular tachycardia (n = 1), premature ventricular complexes (of RV and LV origin) (n = 6), right bundle-branch block (BBB) (n = 5), and first-degree atroventricular block (n = 2).

Echocardiography
Eight cats were studied by echocardiography (Figure 2) as part of their clinical evaluation for CHF or arrhythmias. Marked RA and RV enlargement was evident in each (RV end-diastolic dimension, 17.1 ± 5.9 mm; normal, 5.0 ± 2.1 mm; P < 0.001). Additional abnormalities included paradoxical septal motion (n = 2); abnormal muscular trabecular patterns, particularly in the apical RV cavity (n = 7); and images consistent with localized RV aneurysm formation (ie, akinetic or dyskinetic areas with diastolic outward bulging) in the apical or subtricuspid region (n = 4).

Ventricular septal and LV wall thicknesses at end diastole, LV end-diastolic and end-systolic cavity dimensions, and percent fractional shortening (in the absence of paradoxical septal motion) did not differ significantly from normal control values. LA enlargement was mild (16 to 17 mm) in 5 of 8 cats and severe (24 to 26 mm) in 3 of 8 (normal,
Necropsy Findings

Gross Pathology

Morphological abnormalities were striking and consistent with those previously described in human ARVC patients.\(^1\) In all 12 ARVC cats, moderate-to-severe RV dilatation (Figures 3 and 4) was present.

RV wall thinning (Figures 3 and 4) was either diffuse (\(n=7\)) or segmental (\(n=5\)) and associated with a flattened appearance of RV wall trabeculae; RV septoparietal bands appeared prominent. RV wall thickness in ARVC cats was 1.4 ± 0.3 mm and was reduced compared with 2.3 ± 0.1 mm in controls (\(P<0.001\)) (Table 1). Also, aneurysms were present in apical, subtricuspid, and infundibular regions of the RV wall in 6 of the 12 ARVC cats; these included focal aneurysms (with external bulging) to larger aneurysms that appeared translucent (Figures 3 and 4). Control cats had no evidence of cardiac chamber enlargement, wall thinning, or abnormal trabecular structure (Table 1).

RA cavity dilation was present and severe in 7 of the 12 ARVC cats; portions of RA walls were markedly thinned, facilitating transillumination. LA dilation was also evident in 4 ARVC cats; the thickness of the LA (1.2 ± 0.3 mm) and RA (0.9 ± 0.4 mm) walls did not differ significantly from controls (1.6 ± 0.2 and 1.2 ± 0.3 mm, respectively) (Table 1). Mural thrombosis was observed in 2 ARVC cats (RV apex, Figure 4C, and LA appendage).

The LV chamber appeared grossly normal in all but 2 ARVC cats, in which chamber size was judged to be mildly increased. The thickness of the LV free wall (5.9 ± 1.1 mm) and ventricular septum (5.6 ± 0.9 mm) did not differ significantly from controls (6.6 ± 0.4 and 6.1 ± 0.5 mm, respectively) (Table 1).

Histopathology

Histological lesions also closely resembled those characteristic of human patients with ARVC.\(^1\) Most prominent was...
the evidence of myocardial atrophy in the RV, with cardiac myocytes replaced by adipose or fibrous tissue in 2 patterns: fibrous or fibrofatty (n = 9, 75%) and fatty (n = 3, 25%) (Table 2). The fibrous or fibrofatty pattern consisted of focal or diffuse myocardial atrophy associated with adipose tissue and replacement-type fibrosis and extending from the epicardium toward the endocardium (Figure 5). The fatty pattern within the RV wall and trabeculae was characterized by multifocal areas of adipose cell infiltration with only scant interstitial fibrosis (Figure 6). In both morphological forms, residual surviving myocytes were usually scattered within the areas of fibrosis or fat. Fibrous replacement was present in the LV free wall in 10 ARVC cats, in the ventricular septum in 8, and in the LA and RA walls in 2. Fatty infiltration was present in the LV free wall in 2 ARVC cats but was not observed in the LV free wall and ventricular septum of 8 animals. There

**TABLE 1. Gross Morphological Features in Domestic Cats With ARVC Compared With Controls**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ARVC (n=12)</th>
<th>Controls (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV enlargement*</td>
<td>2.7</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA enlargement*</td>
<td>2.8</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV enlargement*</td>
<td>0.2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>LA enlargement*</td>
<td>1.0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>RV thickness, mm</td>
<td>1.4±0.3</td>
<td>2.3±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA thickness, mm</td>
<td>0.9±0.4</td>
<td>1.2±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LA thickness, mm</td>
<td>1.2±0.3</td>
<td>1.6±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV free wall thickness, mm</td>
<td>5.9±1.1</td>
<td>6.6±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular septal thickness, mm</td>
<td>5.6±0.9</td>
<td>6.1±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>RV aneurysms, No. of cats (%)</td>
<td>6 (50)</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*S Scored on a semiquantitative 0 to 3 scale by gross visual inspection.

Focal or multifocal RV myocarditis (Figure 7) was present in all 9 ARVC cats with the fibrofatty pattern and in 1 of 3 cats with the fatty form of repair but in none of the controls (Table 2). Inflammatory infiltrates were negative for Cd79a and focally positive for CD3 staining and therefore consisted mostly of T lymphocytes associated with myocyte cell death and mild-to-severe fibrous tissue deposition. Similar findings, consistent with patchy inflammatory infiltrates, were also present in the LA and RA walls of 9 ARVC cats, as well as the LV free wall and ventricular septum of 8 animals. There

**TABLE 2. Histopathologic Features in Domestic Cats With ARVC Compared to Controls**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ARVC (n=12)</th>
<th>Controls (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial injury/repair,* No. of cats (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>12 (100)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrous (fibrofatty)</td>
<td>9 (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty</td>
<td>3 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV free wall†</td>
<td>10 (83)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Ventricular septum†</td>
<td>8 (67)</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>LA/RA†</td>
<td>2 (17)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Myocarditis, No. of cats (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>10 (83)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>LA/RA</td>
<td>9 (75)</td>
<td>0</td>
<td>0.009</td>
</tr>
<tr>
<td>LV</td>
<td>8 (67)</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Apoptosis, No. of cats (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (75)‡</td>
<td></td>
<td>0</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Defined as fibrous and fibrofatty tissue formation associated with myocyte loss.
†Fibrofatty variety.
‡Mean apoptotic index (total No. positive myocytes/total No. myocytes×100) was 28±23% in RV, 21±19% in LV, and 17±15% in ventricular septum.
Figure 5. Fibrofatty variant of ARVC in a cat that died with right-sided CHF and ventricular tachycardia. A, Cross section through both ventricles shows transmural scarring of anterior RV wall and patchy fibrosis of ventricular septum. Heidenhain trichrome stain. B, Relatively low-magnification view reveals presence of fatty replacement tissue in RV wall associated with residual myocytes embedded within or bordered by adipose cells, and patchy inflammatory infiltrates consisting of mononuclear cells. Hematoxylin-eosin stain; magnification ×100. C, High-magnification view of section delineated by box in B. Hematoxylin-eosin stain; magnification ×200.
were no statistically significant differences between ARVC cats with or without histopathological evidence of LV involvement (ie, fibrofatty replacement) with respect to age at death, clinical presentation, arrhythmias, atrial involvement, pattern of RV myocardial atrophy (ie, fibrofatty or fatty pattern), presence of RV aneurysms, or myocarditis. There was no difference in the frequency of myocarditis detected in the LV and RV (Table 2).

The epicardium frequently showed tiny areas of fibrous thickening in the fibrofatty cases associated with focal mononuclear infiltrates, mostly at the atrial level. These histological changes were absent from normal controls. Myocyte disarray was not observed in ARVC or control cats. Abnormal intramural small vessels, with thickened walls (due primarily to medial hypertrophy), were observed in only 2 ARVC and 1 control animal.

Apoptosis
Apoptotic myocytes were identified by TUNEL histochemical investigation in 9 of the 12 cats with ARVC (Figure 7C). Mean apoptotic indices were 28±23% in the RV, 21±19% in the LV, and 17±15% in the ventricular septum. No apoptotic cells were detected in normal control cat hearts (Table 2).

Clinical Outcomes
Eight of the 12 cats with ARVC died of (n=6) or were euthanized (n=2) for reasons directly associated with profound right-sided CHF or thromboembolism. The 6 cats that died of CHF had survived 2 days to 4 months (median, 1 month) after clinical onset; 1 of these 6 cats had atrial fibrillation for 6 years before developing CHF. Medical management included diuretics, digitalis, and ACE inhibitors. Of the remaining 4 cats, 2 were euthanized for progressive renal failure, and 2 died of noncardiac causes (erythroid leukemia in 1 and lymphosarcoma in 1).

Discussion
ARVC is a heart muscle disorder of uncertain origin and is characterized by supraventricular and ventricular tachyarrhythmias, sudden cardiac death, and in some patients, CHF.\(^{1-8}\) Although it is relatively uncommon, its novel clin-
ical and pathophysiological features are of great interest to clinicians, given the difficulty often encountered in clinical diagnosis and the propensity of ARVC to cause sudden death in young people (including trained athletes) in some parts of the world.8 Familial forms with autosomal dominant inheritance patterns have been demonstrated.1,4 None theless, neither the specific gene defects nor the defective coded proteins have been identified.

We documented, for the first time, a spontaneously occurring cardiac disease in domestic cats that is remarkably similar to ARVC in humans. Moreover, ARVC had considerable impact on the clinical course of affected animals. Eight of the 12 cats died of progressive right-sided CHF (2 were ultimately euthanized) despite aggressive medical management with diuretics, ACE inhibitors, and digitalis. Although most human patients with ARVC die suddenly and unexpectedly (often without prior symptoms),1,2,4,6–8 marked CHF that may have progressed to heart failure–related death was evident in our cats. Typical right atrial enlargement, atrial dilatation, and RA enlargement were evident, similar to that documented at autopsy. Thus, it appears that careful echocardiographic examination may provide a suitable noninvasive means to identify RV morphology suggestive of ARVC in this feline model. Although other forms of spontaneous cardiomyopathy have been documented in domestic cats,9–12,20 the morphological features in ARVC cats are unique to this condition and have not been reported in other types of feline myocardial disease. To the best of our knowledge, an RV cardiomyopathy has been described previously in only 3 animals (2 dogs and 1 mink).21–23

Our cats with ARVC frequently showed ECG abnormalities similar to those in patients with this disease, including supraventricular tachyarrhythmias (particularly atrial fibrillation), complex ventricular ectopy including ventricular tachycardia, and major conduction abnormalities.1,24,25 The frequency of atrial fibrillation in our ARVC cats was not surprising in view of the severe RA enlargement usually associated with RV dilatation. Because it is not our practice in feline cardiology to routinely record precordial chest leads, we were not able to reliably assess certain ECG characteristics of ARVC in human patients, such as T-wave inversion and epsilon waves.24 Moreover, the damping effects of pleural effusion may have hindered identification of subtle depolarization abnormalities.

At autopsy, ARVC cats demonstrated characteristic morphological hallmarks reported in human patients with this disease.1,6,7 These included marked RV (and RA) cavity enlargement associated with RV wall thinning that was segmental or involved substantial portions of the wall. The apical, subtricuspid, and infundibular regions of the RV wall were usually involved; in some cats, aneurysm formation was evident at these sites. Such aneurysms represent a common and unique feature of this condition in patients with ARVC.1–7

The histopathological findings reported here represent evidence of myocardial cell injury and death as well as repair in the RV, again closely resembling that described in humans.1,6,7 Typically, repair changes took the form of fibrofatty or fatty replacement of myocardium, with the surviving myocytes embedded in replacement tissue. Also, most cats had evidence of myocarditis in the RV as well as in the LV and both atria. We1,7,26 and others2 have postulated a possible pathogenic role for myocarditis in the widespread myocyte damage and repair observed in human ARVC. These observations are supported by the experimental study by Matsumori and Kawai,27 who reported that BALB/c mice infected with coxsackievirus B3 developed selective RV myocarditis with mononuclear cell infiltrates and myocyte death, and later by RV aneurysms. However, direct evidence by reverse transcription–polymerase chain reaction for involvement of enteroviruses in human ARVC is incomplete, having been reported in only a few patients.28 Moreover, we recently performed a study with nested polymerase chain reaction on endomyocardial biopsies in 20 consecutive ARVC patients, which proved negative for the enteroviral genome.29

Of note, the histopathological changes of ARVC were not confined to the RV of our cats. Similar but generally less marked lesions of myocardial injury and repair were also observed in ventricular septum or LV free wall of most animals. LV involvement has also been reported in some human patients, suggesting that the ARVC disease process may progress with time to involve the LV.1,6,19 The morphological changes reported here in domestic cats with ARVC imply a similar course of disease evolution.

Apoptosis was detected in a high percentage of the feline ARVC hearts, with a mean apoptotic index similar to that reported in human ARVC patients.30,31 This finding supports the hypothesis that the pathogenesis of ARVC may depend in part on inflammation as well as programmed cell death. The coexistence of apoptosis and myocarditis in cats with ARVC indicates that these mechanisms contribute to myocyte injury and repair in susceptible felines and suggests that myocarditis may represent a trigger for apoptosis. Indeed, recent experimental studies highlight complex interactions between proapoptotic proteins, proinflammatory cytokines, and other agents that modulate apoptosis and myocarditis and that may adversely affect cardiac structure.32,33 The substantial gross and histological cardiac abnormalities associated with apoptosis and myocarditis reported here are likely to represent the substrate for heart failure and arrhythmias evident both in our feline animal model and in human patients with ARVC.

In summary, feline ARVC as described in this report is remarkably similar to that condition in human patients with respect to both clinical and pathological features, and we have come to regard feline ARVC as the clinical equivalent of ARVC in humans. In particular, we consider this feline model to be a potentially important investigative tool that could enhance our understanding of the complex clinical and pathophysiological mechanisms operative in ARVC, as well as genetic factors and molecular mechanisms responsible for
its genesis. Consequently, spontaneous feline ARVC appears to have substantial value as an animal model of human ARVC.

Acknowledgements
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References
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