Arrhythmogenic Right Ventricular Cardiomyopathy and Fatty Replacement of the Right Ventricular Myocardium
Are They Different Diseases?

Allen P. Burke, MD; Andrew Farb, MD; Gerti Tashko; Renu Virmani, MD

Background—The relationship between arrhythmogenic right ventricular cardiomyopathy (ARVC) and pure fat replacement of the right ventricle is unclear.

Methods and Results—Myocardial thickness, epicardial fat thickness, percent fibrosis, and intramyocardial fat infiltration were measured in 16 sections each from 25 hearts with typical (fibrofatty) ARVC, 7 hearts with fat replacement of the right ventricle without fibrosis (FaRV), and 18 control hearts from patients who died of noncardiac causes. Patients with fibrofatty ARVC were younger than those with FaRV (31 ± 14 versus 44 ± 13 years, P = .02), more likely to have a history of arrhythmias or a family history of premature sudden death (56% versus 0%, P = .01), more likely male (80% versus 29%, P = .02), and less likely to have coexisting conditions that might have predisposed to sudden death (12% versus 86%, P < .001). Fibrofatty ARVC was characterized by right ventricular myocardial thinning, fat infiltration of the anterobasal and posterolateral apical right ventricle, subepicardial left ventricular fibrofatty replacements (64%), myocyte atrophy (96%), and lymphocytic myocarditis (80%). FaRV showed normal or increased myocardial thickness, a diffuse increase in intramyocardial and epicardial fat, little inflammation, and an absence of myocardial atrophy. Intramyocardial fat was frequently seen in normal hearts, especially in the anterobasal region, but was less extensive than in fibrofatty ARVC and FaRV.

Conclusions—ARVC is a familial arrhythmogenic disease characterized by fibrofatty replacement of myocytes with scattered foci of inflammation. Fat infiltration per se is probably a different process that should not be considered synonymous with ARVC. (Circulation. 1998;97:1571-1580.)

Key Words: arrhythmia • death, sudden • cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined clinically by abnormalities of conduction, repolarization and depolarization, ventricular arrhythmias, family history, and structural abnormalities of the right ventricle.1-3 Arrhythmias that characterize ARVC include idiopathic ventricular fibrillation, ventricular extrasystoles, supraventricular tachycardia,4 and ventricular tachycardia of right ventricular origin (with a left bundle-branch pattern).5 Clinical identification of right ventricular structural abnormalities includes regional hypokinesia and segmental bulging or global hypokinesia of the right ventricle at echocardiography or right ventricular angiography.6

See page 1532

Only a few autopsy studies have characterized the morphological alterations in ARVC,3,7,8 and pathological data on cases from the United States are relatively scarce. Two pathological types of ARVC have been proposed: typical ARVC with fat infiltration and scarring (fibrofatty ARVC) and a form of ARVC characterized solely by fat replacement (FaRV).8 The designation of a purely fatty form of ARVC is problematic, however, because it has long been appreciated (and recently documented by quantitative study) that significant fat infiltration of the right ventricle occurs in >50% of normal hearts in elderly patients.9,10 Morphometric analysis of biopsy sections showed a greater amount of fibrous tissue in young patients and a greater prevalence of fatty tissue in adults.11 The presence of fatty tissue and fibrous tissue exceeding 3.21% and 40.38%, respectively, has been considered highly suspect for arrhythmogenic right ventricular cardiomyopathy in right ventricular endomyocardial biopsy.12 However, no autopsy study has quantified the relative amounts of fibrous tissue and fat in hearts with ARVC.

The purpose of this study is to evaluate the gross and histological features of two types of fat replacement of the right ventricle: fibrofatty ARVC and FaRV. A morphological comparison of these two entities with a group of controls...
hearts will help to determine whether there are distinct pathological differences separating them.

Methods

Case Selection
All cases in the gross heart repository at the Armed Forces Institute of Pathology between the years 1970 and 1996 were searched for the following two criteria entered into the computerized diagnostic database: fat infiltration or fibrofatty infiltration of the right ventricle and sudden unexpected death or cardiomyopathy. Upon review of systematic tissue evaluation (see below), cases were retained if there was fibrofatty replacement in at least two sections of right ventricle or >50% fat replacement in at least one right ventricular section of the basal or posterior right ventricle. A total of 35 cases were retrieved, of which 5 were excluded. The basis of exclusion was inadequate tissue (n=2) or inadequate diagnostic criteria of FaRV or fibrofatty ARVC (n=3). Thirteen control hearts were selected consecutively as trauma controls, and an additional 5 controls were selected on the basis of obesity (body mass index >39 kg/m²) and a noncardiac cause of death. The obese controls were included for accounting of increased fat content due to obesity.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fibrofatty ARVC</th>
<th>FaRV</th>
<th>Control Subjects</th>
<th>P, Fibrofatty vs FaRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>7</td>
<td>18</td>
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<tr>
<td>Age, y (mean±SD)</td>
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<td>44±13</td>
<td>36±12</td>
<td>.02</td>
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<td>Sex, male:female</td>
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<td>.02</td>
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<td>History of arrhythmias, n (%)</td>
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<td>.07</td>
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<tr>
<td>Family history of sudden unexpected death, n (%)</td>
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<td>0</td>
<td>.30</td>
</tr>
<tr>
<td>Family or patient history of arrhythmias, n (%)</td>
<td>14 (56)</td>
<td>0</td>
<td>0</td>
<td>.01</td>
</tr>
<tr>
<td>Death during exercise, n (%)</td>
<td>14 (56)</td>
<td>0</td>
<td>0</td>
<td>.01</td>
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<tr>
<td>Mean heart weight, g</td>
<td>432±70</td>
<td>481±120</td>
<td>433±137</td>
<td>.15</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; FaRV, fatty replacement of right ventricular myocardium.

Figure 1. Fibrofatty arrhythmogenic right ventricular cardiomyopathy. A, Marked right ventricular dilatation. Patient was a 13-year-old boy who died suddenly without history of arrhythmias or family history. B, Higher magnification demonstrates apical aneurysm characterized by myocardial thinning (arrow) and gross fat infiltrates (arrowheads). C, Histologically, area of fat infiltration demonstrated predominantly fat. D, Higher magnification of C demonstrates, in addition to fat, large amounts of fibrous tissue (gray areas).
### Table 2. Right Ventricular Myocardial Thickness, Excluding Epicardial Fat: ARVC, FaRV, and Control Subjects

<table>
<thead>
<tr>
<th>Site</th>
<th>Fibrofatty ARVC</th>
<th>Control Subjects</th>
<th>FaRV</th>
<th>P, Fibrofatty ARVC vs Control Subjects</th>
<th>P, FaRV vs Fibrofatty ARVC</th>
<th>P, FaRV vs Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 6 areas</td>
<td>2.0±0.8</td>
<td>2.7±0.4</td>
<td>3.1±0.8</td>
<td>.004</td>
<td>.0006</td>
<td>.15</td>
</tr>
<tr>
<td>Anterior base</td>
<td>2.4±1.3</td>
<td>3.3±0.8</td>
<td>3.9±0.9</td>
<td>.01</td>
<td>.003</td>
<td>.25</td>
</tr>
<tr>
<td>Lateral base</td>
<td>2.2±1.0</td>
<td>3.0±0.9</td>
<td>4.1±2.2</td>
<td>.05</td>
<td>.0008</td>
<td>.05</td>
</tr>
<tr>
<td>Posterior base</td>
<td>2.5±1.1</td>
<td>3.5±1.0</td>
<td>3.6±1.1</td>
<td>.04</td>
<td>.10</td>
<td>.91</td>
</tr>
<tr>
<td>Anterior apex</td>
<td>1.2±0.6</td>
<td>1.9±1.1</td>
<td>2.5±1.0</td>
<td>.004</td>
<td>.0005</td>
<td>.13</td>
</tr>
<tr>
<td>Lateral apex</td>
<td>1.3±0.7</td>
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<td>.002</td>
<td>.02</td>
<td>.91</td>
</tr>
<tr>
<td>Posterior apex</td>
<td>1.7±1.1</td>
<td>2.4±0.9</td>
<td>2.9±1.1</td>
<td>.02</td>
<td>.01</td>
<td>.38</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are mm±SD.

The study was designed to provide a wide range of body mass to investigate the role of body fat on myocardial fat infiltration. Cases were considered FaRV if no significant fibrosis was noted with Masson’s trichrome stain, verified by morphometric analysis of <5% fibrous tissue in any of the sections examined (see below).

### Tissue Evaluation

In every case, the heart was reexamined for the purpose of this study. The original heart weights were recorded, and 16 sections were taken from each heart in a uniform fashion. Four sections were taken from the right ventricular base (anterior, anterolateral, posterolateral, and posterior), four from the right ventricular apex (anterior, anterolateral, posterolateral, and posterior), four from the basal left ventricle (anterior, lateral, posterior, and septal), and four from the left ventricle near the apex (anterior, lateral, posterior, and septal). The myocardial thickness and epicardial fat thickness were measured grossly in each section to the nearest 0.5 mm. In cases in which the epicardial-myocardial junction was difficult to ascertain grossly, measurements were made in conjunction with histological sections, allowing for 25% shrinkage artifact due to processing.

Each section was stained with Masson’s trichrome stain and hematoxylin-eosin. The degree of fibrosis and fat was quantified by computerized morphometry of each Masson’s trichrome–stained section. With these sections, the percent area of azurophilic staining (fibrosis) and white staining (fat) was ascertained in ×2 (for fat) and multiple ×10 (for fibrosis) objective fields showing representative areas of myocardium spanning the endocardium to epicardium. The higher magnification was used for fibrosis determinations because color separation was technically more difficult for fibrous tissue than for fat. Care was taken to avoid areas with artifactual spaces or large vascular lumina that would be interpreted as fat and to include only areas that were entirely intramyocardial to exclude epicardial or perivascular fat. Morphometric measurements of the myocardial fibrous tissue were performed on digitized images (IPLab Spectrum image processing software, Signal Analytics Corp). Color separations used to define fibrous tissue were configured. Color-mapped images were inspected for accuracy, and computerized morphometric area measurements were performed. All morphometric observations and measurements were made by one of us without knowledge of the diagnosis.

Inflammatory foci (myocarditis) were defined by the Dallas criteria and quantified for each case. The avidin-biotin complex method was applied to deparaffinized sections of tissues from 7 cases of fibrofatty ARVC. Sections were stained with OPD4 (CD4 marker, 1:50 dilution) and CD8 (1:50 dilution) (Dako Corp). Myocyte atrophy was defined as myocyte vacuolization with large areas of myofibrillar loss.

The endocardial, midzonal, or epicardial distribution of right ventricular intramyocardial fat, intermingling of fat and fibrous tissue, or replacement fibrosis was determined in each area section. Endocardium was defined as present within 0.5 mm of the endothelial surface, as determined by ocular micrometer.

### Statistical Evaluation

Mean myocardial thickness, epicardial fat thickness, percent fat infiltration, and fibrous tissue infiltration were calculated for each

**Figure 2.** Fibrofatty arrhythmogenic right ventricular cardiomyopathy. A, Dilatation of right ventricular outflow area with fat infiltrates of ventricular wall (arrowheads). B, Histologically, admixture of fat and fibrous tissue.
Epicardial Fat in Right Ventricle: Gross Mean Thickness by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Fibrofatty ARVC</th>
<th>Control Subjects</th>
<th>FaRV</th>
<th>P, ARVC vs Control Subjects</th>
<th>P, FaRV vs Fibrofatty ARVC</th>
<th>P, FaRV vs Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 6 areas</td>
<td>1.8±1.0</td>
<td>1.5±0.8</td>
<td>3.9±2.3</td>
<td>.3</td>
<td>.0004</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anterior base</td>
<td>1.9±1.4</td>
<td>0.7±1.1</td>
<td>3.6±3.3</td>
<td>.01</td>
<td>.03</td>
<td>.0003</td>
</tr>
<tr>
<td>Lateral base</td>
<td>2.1±1.7</td>
<td>1.9±0.8</td>
<td>3.6±1.9</td>
<td>.5</td>
<td>.02</td>
<td>.01</td>
</tr>
<tr>
<td>Posterior base</td>
<td>1.3±1.7</td>
<td>1.1±1.2</td>
<td>2.7±2.2</td>
<td>.5</td>
<td>.08</td>
<td>.01</td>
</tr>
<tr>
<td>Anterior apex</td>
<td>2.1±1.4</td>
<td>2.2±1.5</td>
<td>5.7±3.2</td>
<td>.9</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lateral apex</td>
<td>2.2±1.2</td>
<td>2.0±1.1</td>
<td>4.6±2.7</td>
<td>.6</td>
<td>.0006</td>
<td>.0003</td>
</tr>
<tr>
<td>Posterior apex</td>
<td>1.5±1.4</td>
<td>1.1±1.1</td>
<td>3.3±4.0</td>
<td>.2</td>
<td>.04</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are mm±SD.

Results

Patient Characteristics

Fibrofatty ARVC

The mean age of patients with fibrofatty ARVC was 31 years (range, 13 to 72 years) (Table 1). There were 20 male and 5 female patients, and 10 (40%) had a history of arrhythmias or syncope; in no patient was the diagnosis of ARVC made during life. Death was sudden in 23 cases (all of which were referred to medical examiners’ offices). Death occurred during exercise in 14 cases (56%). The sporting activities were basketball (n=11), running (n=2), and baseball (n=1). A family history of premature sudden death in a first-degree family member <35 years old was elicited in 7 cases (28%), although in no case was there a documented family history of ARVC. There were possible contributing factors to cardiac arrhythmias in 3 patients: 2 had a history of alcohol abuse and 1 of intravenous drug abuse (although toxicological analysis was negative at the time of death). There were no other significant medical conditions by clinical history or autopsy examination in any patient. In 2 cases, death occurred in the hospital after a period of heart failure. One patient was a 41-year-old man admitted for shortness of breath who was found dead in his room; heart findings showed mild cardiomegaly, moderate right ventricular dilatation, multifocal inflammatory infiltrates, and an absence of left ventricular involvement. The other patient with heart failure was 71 years old (the oldest in the group) and had extensive left ventricular involvement in the form of subepicardial scars; inflammation was absent.

FaRV

The mean age of patients with FaRV was 44±13 years (significantly older than those with fibrofatty ARVC, P=.02). Only 2 of 7 patients were male (P=.02 versus fibrofatty ARVC). No patient had a history of arrhythmias or a family history of sudden death. Three deaths occurred when the patient was at rest (presumably asleep), and 4 patients were...
performing nonstrenuous activity (1 driving an automobile, 1 working at a desk, and 2 performing household activities). Although death may have been a cardiac arrhythmia due to FaRV, there were one or more contributing factors to sudden death in 6 of 7 cases. Two patients suffered from asthma, 1 had mitral valve prolapse (autopsy diagnosis), 1 had focal coronary atherosclerosis with 75% cross-sectional lumenal narrowing of the left anterior descending coronary artery (autopsy diagnosis), 1 had a seizure disorder, and 1 had a history of alcohol abuse with fatty liver at autopsy. One patient had insulin-dependent diabetes mellitus, but there was no evidence of elevated glucose or ketones at postmortem evaluation of vitreous humor. One patient was diagnosed with Laurence-Moon-Biedl syndrome and was moderately obese (196 lb, 5 ft 5 in tall); fatty liver was found at autopsy. Another patient was moderately obese (168 ± 41 lb (range, 111 to 240 lb), with a mean body mass index of 36.4 ± 6.3 kg/m². By established criteria based on body mass index, 2 of these patients would be considered moderately obese, 1 mildly obese, and 4 normal weight.

Control Subjects
The mean age of the control subjects was 36 ± 13 years. The causes of death were vehicular trauma (n=9), gunshot wounds (n=5), pulmonary embolism (n=2), and sleep apnea associated with morbid obesity (n=2). The mean body weight for control subjects was 173 ± 32 lb for nonobese and 331 ± 68 lb for obese subjects. No structural abnormalities of the heart or evidence of significant coronary atherosclerosis was present in control subjects.

Myocardial Thickness
Fibrofatty ARVC was characterized by areas of myocardial thinning located throughout the right ventricle. Apical aneurysms were present in 13 hearts (Fig 1), basilar aneurysms in 8, and multiple aneurysms in 3; in 1 heart, there was no evidence of ventricular dilatation or thinning. Right ventricular dilatation was absent in 1 heart, mild in 5, moderate in 10, and severe in 9. When the myocardial exclusive of epicardial fat was measured, there was a significant decrease in mean thickness between fibrofatty ARVC and both FaRV and normal control hearts in virtually all areas of right ventricle (Table 2). However, in some areas of maximal involvement, there was no appreciable gross thinning (Fig 2).

FaRV was characterized by a slight increase in myocardial thickness compared with control hearts in all areas of right ventricle, although the differences were not significant. Mild right ventricular dilatation was noted in 2 hearts, and the right ventricle did not appear to be dilated in 5.

Epicardial Fat Thickness
Epicardial fat was not significantly increased in fibrofatty ARVC in most areas of the right ventricle (Table 3). Only in the outflow tract area was there an increase in epicardial fat compared with controls (mean, 1.9 versus 0.7 mm, P=.01). FaRV was characterized by an increase in epicardial fat in all areas of the right ventricle compared with controls and was significantly increased compared with fibrofatty ARVC in all areas of the right ventricle except for the posterior base (Table 3).

There was no correlation between epicardial fat thickness and body weight in the control group. The mean epicardial fat thickness for all areas in the right ventricle combined was identical (1.5 ± 0.8 mm for nonobese and obese controls). There was no correlation between body weight and epicardial fat thickness in any area examined (r² = .0005 to .08, P=.14 to .97).

Morphometric Intramyocardial Fat Measurements
In control hearts, the degree of right ventricular intramyocardial fat was greatest in the anterior apex (Fig 3), with a mean of 15%, and was least in the right ventricular outflow region and posterior basal right ventricle (Table 4). FaRV hearts were characterized by a statistically significant increase in fat in all areas versus controls (Fig 4), with the greatest increase in the lateral apex. The degree of fat infiltration in fibrofatty ARVC, although consistently greater than that of control hearts, was significantly increased only in the anterior base and lateral apex.

In the ventricular septum, mean fat replacement did not exceed 3% in any group. However, there was a statistically significant increase in fat in fibrofatty ARVC compared with controls (Table 4) in both the apical and basal regions.

### Table 4. Myocardial Fat Infiltration in the Right Ventricle by Computerized Morphometric Analysis

<table>
<thead>
<tr>
<th>Site</th>
<th>ARVC</th>
<th>Control Subjects</th>
<th>FaRV</th>
<th>P, FaRV vs Control Subjects</th>
<th>P, FaRV vs Fibrofatty ARVC</th>
<th>P, FaRV vs Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 6 areas</td>
<td>17 ± 11</td>
<td>10 ± 8</td>
<td>32 ± 10</td>
<td>.02</td>
<td>.0007</td>
<td>&lt; .0001</td>
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<tr>
<td>Anterior base</td>
<td>18 ± 16</td>
<td>7 ± 7</td>
<td>32 ± 10</td>
<td>.004</td>
<td>.009</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Lateral base</td>
<td>17 ± 12</td>
<td>11 ± 11</td>
<td>33 ± 12</td>
<td>.15</td>
<td>.002</td>
<td>.001</td>
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<td>Basal septum</td>
<td>1.4 ± 1.7</td>
<td>0.4 ± 1.0</td>
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<td>.07</td>
<td>.27</td>
<td>.02</td>
</tr>
<tr>
<td>Anterior apex</td>
<td>18 ± 14</td>
<td>15 ± 13</td>
<td>32 ± 18</td>
<td>.45</td>
<td>.03</td>
<td>.01</td>
</tr>
<tr>
<td>Lateral apex</td>
<td>22 ± 15</td>
<td>11 ± 11</td>
<td>38 ± 13</td>
<td>.01</td>
<td>.01</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Posterior apex</td>
<td>16 ± 17</td>
<td>7 ± 7</td>
<td>33 ± 20</td>
<td>.08</td>
<td>.01</td>
<td>.0004</td>
</tr>
<tr>
<td>Apical septum</td>
<td>2.2 ± 2.6</td>
<td>0.2 ± 0.5</td>
<td>1.4 ± 3.1</td>
<td>.004</td>
<td>.4</td>
<td>.21</td>
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</tbody>
</table>
In the left ventricle, fibrofatty ARVC was characterized by a small but significant increase in intramyocardial fat infiltration (generally in a subepicardial location) in all areas compared with control hearts. The mean percent fat replacement in the six areas of left ventricle was 0.4±0.3% in controls, 5.1±3.3% for fibrofatty ARVC (P<.0001 versus controls), and 2.3±2.2% for FaRV (P=.002 versus controls). In FaRV, a significant increase in intramyocardial left ventricular fat compared with controls was limited to the anterior wall and posteroapical areas of the left ventricle.

**Fibrous Tissue**

In fibrofatty ARVC, fibrous tissue was generally intermingled with fat, and in only one case was there prominent fibrosis in areas with little fat replacement. The percent fibrous tissue in right ventricular sections in cases of fibrofatty ARVC was 17±16% (anterobasal), 18±16% (basolateral), 17±13% (posterobasal), 15±13% (anteroapical), 15±13% (apicolateral), and 13±12% (posteroapical). There was no significance between any region (paired t test, P>.4 between all pairs). Areas of left ventricular subepicardial fibrosis (>10% fibrous tissue) were present in 16 of 25 cases of fibrofatty ARVC (Fig 5), 0 of 7 cases of fatty infiltration, and 1 of 18 controls (Table 5). The sites of maximal fibrosis in the left ventricle in the 16 cases of fibrofatty ARVC were posterior base (4 cases), anterior base (2 cases), lateral base (2 cases), lateral apex (1 case), anterior apex (1 case), and apical septum (2 cases).

In 24 of 25 cases of fibrofatty ARVC, vacuolated myocytes with prominent myofibrillar loss were present in right ventricular areas of fibrosis (Table 5) (Fig 6). Myofibrillar loss was seen in 1 of 18 controls, in a heart from a patient with morbid obesity. Vacuolated cells with myofibrillar loss were not present in cases of FaRV.

**Distribution of Fat and Fibrous Tissue in the Right Ventricle**

A mixture of fibrous tissue and fat, characteristic of fibrofatty ARVC, was present in any endocardial region (within 0.5 mm of the endothelial surface) in 19 of 25 hearts (72%) with fibrofatty ARVC; in three cases, the areas of fibrofatty intermingling were midzonal (Fig 6) and in three cases, mostly subepicardial. Of the total 200 sites examined, 42% demonstrated endocardial fibrofatty intermingling, 29% endocardial replacement fibrosis with myocyte atrophy, and 6% fat infiltration only; in 22%, the endocardium was normal. By site, endocardial fibrofatty areas were present in 62% of the lateral wall (apex and base), 40% of the apical anterior wall, 36% of the anterior and posterior basal right ventricle, and 32% of the posterior apical regions.

Endocardial fat replacement in any area was present in all 7 cases of FaRV (65% of all sections examined) and in 8 of 18 control sections (44%) (23% of all sections examined). The mean number of sections with endocardial fat (within 0.5 mm of the endothelial surface) was 5.3±2.1 for FaRV versus 1.8±2.0 for controls (P<.001) and 3.3±2.3 for fibrofatty ARVC (P=.03 versus controls). The regions most likely to contain endocardial fat in FaRV were the lateral basal and lateral apical wall (6 of 7 hearts) and the least likely...
regions the basal posterior wall (3 of 7 hearts). In controls, the region most likely to contain endocardial fat was the anterior apex (6 of 18 hearts) and the least likely regions the lateral and posterior basal walls (each, 2 of 18 hearts).

**Inflammatory Infiltrates**

Inflammatory infiltrates with focal myocyte necrosis were present within the myocardium of 20 of 25 cases of fibrofatty ARVC (Fig 7), 1 of 7 cases of FaRV, and 1 of 18 controls (Table 5). In fibrofatty ARVC, they were exclusively in the right ventricle in 14 cases, biventricular in 5, and only in the left ventricle in 1. The mean number of necroinflammatory foci was 6.3 ± 8.0 (range, 1 to 35) in the 16 sections examined in cases of fibrofatty ARVC; the FaRV and control cases each had only 1 necroinflammatory focus. In 8 cases of fibrofatty ARVC, the infiltrate was predominantly CD4 cells in 7 (Fig 8) and a mixture of CD4 and CD8 cells in 1.

**Relationships Between Age and Histological Parameters in Fibrofatty ARVC**

There was no correlation between age and maximal percent fibrosis in the right ventricle ($r^2 = .002, P = .8$). There was a significant negative correlation between age and mean right ventricular percent fibrosis of all 8 sections examined ($r^2 = .3, P = .016$). Individuals with left ventricular fibrosis were similar in age (30 ± 12 years) to those without (32 ± 17 years, $P = .7$). There was no correlation between the number of inflammatory foci and age ($r^2 = .01, P = .6$), but the mean age of individuals with inflammation was significantly younger (27 ± 11 years) than those without (42 ± 18 years, $P = .03$). There was no correlation between age and mean percent fat infiltration in the four apical right ventricular sections ($r^2 = .15, P = .10$) and no correlation between mean percent fat infiltration in the four basal right ventricular sections ($r^2 = .07, P = .25$).

**Discussion**

**Fibrofatty ARVC**

The present study demonstrates that the primary features of fibrofatty ARVC are replacement fibrosis and myocyte atrophy, which may occur in virtually any area of the right ventricle and generally result in myocardial thinning. Intramyocardial fat infiltration is most extensive, compared with control hearts, in the right ventricular outflow tract and lateral apex. In the anteroapical right ventricle, there was no significant difference in fat infiltration between fibrofatty ARVC and controls because of the normal large degree of fat infiltration (mean, 15%) in this region of the heart. Epicardial fat is not significantly increased in fibrofatty ARVC, with the exception of the right ventricular outflow, which is also the site of the greatest increase in intramyocardial fat replacement.

For diagnostic purposes, these data indicate that the site of fat measurement influences the significance of increased percent fat composition of the ventricle. Whereas a 15% fat replacement is distinctly abnormal in the right ventricular outflow or posterior walls, it is probably normal in the anterior wall near the apex. The data in the present study corroborate those of Fontaliran et al, who demonstrated that right ventricular fat infiltration is a frequent normal finding in elderly patients and should not be equated with cardiomyopathy. However, the data in the present study also demonstrate that an intermingling of fibrous and fatty tissue (not merely the presence of fat), which is specific for fibrofatty ARVC, is present near the endocardial surface in a high

### Table 5. Left Ventricular Fibrofatty Infiltrates, Inflammation, and Myocyte Atrophy: Fibrofatty ARVC, FaRV, and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Fibrofatty ARVC</th>
<th>Control Subjects</th>
<th>FaRV vs Control Subjects</th>
<th>Fibrofatty ARVC vs FaRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular fibrofatty infiltrates, n (%)</td>
<td>16/25 (64)</td>
<td>1/18 (6)</td>
<td>0/7 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any myocarditic foci, n (%)</td>
<td>20/25 (80)</td>
<td>1/18</td>
<td>1/7 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of myocarditic foci, mean±SD</td>
<td>6.3±8.0</td>
<td>0.1±0.2</td>
<td>0.3±0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocyte vacuolization with atrophy, n (%)</td>
<td>24/25 (96)</td>
<td>1/18 (6)</td>
<td>0/7 (0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
percentage of right ventricular sites (72% of all areas examined) and that endocardial fat alone is much more prevalent in FaRV than in normal control hearts. Therefore, the site of biopsy, as well as the distribution of fat in the right ventricular wall, may influence the sensitivity and specificity of biopsy diagnosis of ARVC.

The present study shows that a high proportion of cases of fibrofatty ARVC demonstrate lymphocytic myocarditis. The high prevalence of myocarditis (80%) may be due to an increase in the sensitivity of detection because of the generous myocardial sampling. Because myocardial inflammation was more prevalent in younger patients with fibrofatty ARVC, we postulate that inflammation may be found in earlier forms of the disease, which may later progress to scarring. Alternatively, younger patients dying with fibrofatty ARVC may have a more lethal or aggressive form of the disease characterized by myocardial inflammation. Although it was not significant, there was also a trend toward a decrease in fibrous tissue and intramyocardial fat in older individuals with fibrofatty ARVC, suggesting that aggressive forms of the disease may result in early sudden death. The large percentage of cases of fibrofatty ARVC in the present study...
supports the concept that in many cases, fibrofatty ARVC is an end stage of a remote inflammatory process, with increased cell death possibly due to apoptosis. However, this study does not rule out the possibility that inflammation is a superimposed process, as favored by Fontaine et al. It remains to be proven whether fibrofatty ARVC is ever the result of a previous viral infection, as molecular studies for enteroviral RNA suggest in a small proportion of cases of idiopathic dilated cardiomyopathy.

The present study demonstrates that with extensive sampling of the left ventricular myocardium, fibrofatty replacement of the epicardium may be found in a majority of cases of fibrofatty ARVC. The regional distribution of fibroinflammatory lesions in fibrofatty ARVC primarily in the right ventricle and secondarily in the left ventricular epicardial location is characteristic of the disease. The etiology of this distribution remains unknown.

**Fat Infiltration of the Right Ventricle**

Fat infiltration of both ventricles without associated scarring has been anecdotally associated with sudden cardiac death and is not necessarily considered a form of ARVC. In the present study, we identified 23% of all cases as FaRV without fibrosis, compared with 40% of cases of ARVC studied at autopsy classified as FaRV in Italy. Although we did not find exertion-related deaths or a family history of sudden death in FaRV, there were no apparent differences in the frequency of exertion at the time of death between FaRV and fibrofatty ARVC in the study by Basso et al. The reason for the relatively small proportion of cases of FaRV in the present study and the differences in clinical findings between ARVC and FaRV in the United States and Europe may be geographic variations, the selection of cases biased toward sudden unexpected death, and the thorough sampling of the right ventricular myocardium, which may have revealed small areas of fibrosis that could be overlooked with limited histological analysis. Indeed, in some cases of fibrofatty ARVC, there may be large areas that grossly appear as pure
fat infiltration, but with adequate sampling of myocardial tissue, fibrous tissue and inflammation may be found.

The significant differences in our data between fibrofatty ARVC and FaRV with regard to sex distribution, frequency of inflammation, presence of myocardial aneurysms, left ventricular involvement, degree of epicardial fat, exertion-related death, and frequency of arrhythmias lead us to surmise that it may be premature to consider fatty and fibrofatty related death, and frequency of arrhythmias lead us to surmise that it may be premature to consider fatty and fibrofatty ARVC as necessarily parts of the same disease spectrum. Indeed, the normal or increased myocardial thickness, reduced frequency of left ventricular involvement, and lack of inflammation in the fatty form of ARVC further support the hypothesis that FaRV is a different entity from ARVC.

The present study demonstrates that significant degrees of fat infiltration are common in the normal right ventricle, especially in the anteroapical region. The mean percent fat infiltration in normal hearts in this study was higher than that found in studies of endomyocardial biopsies but similar to that found in an autopsy study.9

Limitations of the Study

Previous series of ARVC have included a significant proportion of clinically evaluated patients whose initial presentation was not sudden death.2,8 Therefore, the findings in this autopsy study do not necessarily reflect the entire range of pathological findings that represent ARVC. This limitation reflects the broader limitation inherent in autopsy studies, which are inherently biased by case selection and are weighted toward lethal variants of the disease and toward those patients who die suddenly and are likely to undergo postmortem examination.

The limitations of the methodology of this study warrant comment. Because quantification of full-thickness fat replacement was best determined at low magnification and estimations of fibrous tissue were morphometrically feasible only at higher magnifications, the values for fat and fibrous tissue replacement in this study may not be comparable. The purpose of these measurements was to compare the values of each tissue type among the three groups (control, FaRV, and fibrofatty ARVC), and they were done uniformly and in a blinded fashion to detect any pathological differences. The measurements are not intended as diagnostic criteria on smaller tissue samples, such as endomyocardial biopsies, that do not sample large cross sections of ventricular wall.

Conclusions

With thorough myocardial sampling, most cases of ARVC in the United States are of the fibrofatty variety, which differ from FaRV without scarring by the gross features (myocardial thinning versus normal or thick right ventricular walls) and microscopic findings (presence of inflammation and myocardite atrophy). The data in the present study suggest that fat replacement is less arrhythmogenic than typical ARVC. We prefer to render a diagnosis of ARVC only if there is fibrosis, and we believe that at this time, FaRV may be considered a distinct clinicopathological entity and is not necessarily a cause of arrhythmogenic death if identified at autopsy.

References


Arrhythmogenic Right Ventricular Cardiomyopathy and Fatty Replacement of the Right Ventricular Myocardium: Are They Different Diseases?
Allen P. Burke, Andrew Farb, Gerti Tashko and Renu Virmani

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