Spectrum of Clinicopathologic Manifestations of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: A Multicenter Study

DOMENICO CORRADO, MD, CRISTINA BASSO, MD, GAETANO THIENE, MD, FESC, WILLIAM J. McKENNA, MD, FESC, FACC,* MICHAEL J. DAVIES, MD, FESC, FACC,* FABRICE FONTALIRAN, MD,† ANDREA NAVA, MD, FURIO SILVESTRI, MD,‡ CARINA BLOMSTROM-LUNDQVIST, MD,§ ELZBIETA K. WLODARSKA, MD,‖ GUY FONTAINE, MD, PhD, FESC, FACC,‡ FULVIO CAMERINI, MD, FESC‡

Padua and Trieste, Italy; London, England, United Kingdom; Paris, France; Uppsala, Sweden; and Warsaw, Poland

Objective. The aim of the present investigation was to redefine the clinicopathologic profile of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC), with special reference to disease progression and left ventricular (LV) involvement.

Background. Long-term follow-up data from clinical studies indicate that ARVC is a progressive heart muscle disease that with time may lead to more diffuse right ventricular (RV) involvement and LV abnormalities and culminate in heart failure.

Methods. Forty-two patients (27 male, 15 female; 9 to 65 years old, mean [±SD] age 29.6 ± 18) from six collaborative medical centers, with a pathologic diagnosis of ARVC at autopsy or heart transplantation, and with the whole heart available, were studied according to a specific clinicomorphologic protocol.

Results. Thirty-four patients died suddenly (16 during effort); 4 underwent heart transplantation; 2 died as a result of advanced heart failure; and 2 died of other causes. Sudden death was the first sign of disease in 12 patients; the other 30 had palpitations, with syncope in 11, heart failure in 8 and stroke in 3. Twenty-seven patients experienced ventricular arrhythmias (ventricular tachycardia in 17), and 5 received a pacemaker. Ten patients had isolated RV involvement (group A); the remaining 32 (76%) also had fibrofatty LV involvement that was observed histologically only in 15 (group B) and histologically and macroscopically in 17 (group C). Patients in group C were significantly older than those in groups A and B (39 ± 15 years vs. 20 ± 8.8 and 25 ± 9.7 years, respectively), had significantly longer clinical follow-up (9.3 ± 7.3 vs. 1.2 ± 2.1 and 3.4 ± 2.2 years, respectively) and developed heart failure significantly more often (47% vs. 0 and 0, respectively). Patients in groups B and C had warning symptoms (80% and 87%, respectively, vs. 30%) and clinical ventricular arrhythmias (73% and 82%, respectively, vs. 20%) significantly more often than patients in group A. Hearts from patients in group C weighed significantly more than those from patients in groups A and B (500 ± 150 g vs. 328 ± 40 and 380 ± 95 g, respectively), whereas hearts from both group B and C patients had severe RV thinning (87% and 71%, respectively, vs. 20%) and inflammatory infiltrates (73% and 88%, respectively, vs. 30%) significantly more often than those from group A patients.

Conclusions. LV involvement was found in 76% of hearts with ARVC, was age dependent and was associated with clinical arrhythmic events, more severe cardiomegaly, inflammatory infiltrates and heart failure. ARVC can no longer be regarded as an isolated disease of the right ventricle.

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collaborative medical centers with clinicopathologic experience in ARVC participated in the investigation.

### Methods

The study group included 42 hearts of patients with a pathologic diagnosis of ARVC at postmortem examination or after heart transplantation. Only whole hearts available for detailed morphologic investigation of both ventricles and the septum were studied. Incomplete native hearts, partial surgical resections or endomyocardial biopsy specimens, even though morphologically consistent with ARVC, were ruled out. Hearts were included in the study if they exhibited transmural loss of RV musculature with fibrofatty replacement, either regional or diffuse, in the absence of significant coronary artery disease or other known causes and irrespective of the severity of coexistent LV involvement.

The study was carried out in the setting of a cooperative European investigation that included six collaborative medical centers: University of Padua, Padua, Italy (19 cases); University of Trieste, Trieste, Italy (9 cases); Hôpital J. Rostand, Paris, France (6 cases); St. George’s Hospital, University of London, London, England, United Kingdom (6 cases); University of Uppsala, Uppsala, Sweden (1 case); University of Warsaw, Warsaw, Poland (1 case). Clinical history and heart morphology were evaluated according to a specific clinicopathologic protocol developed by the Task Force of the International Society of the Federation of Cardiology. Data were collected in a central registry and recorded in a database for computerized analysis.

**Clinical data.** Retrospective clinical information included patient age and gender, family history of premature sudden death (age <40 years) or ARVC, symptoms at clinical presentation and during follow-up, physical examination, 12-lead electrocardiographic (ECG) changes, arrhythmias, echocardiographic and angiographic findings, drug therapy and circumstances and cause of death.

**Sudden death** was defined as an unexpected natural phenomenon in which loss of all vital functions occurred instantaneously or within 1 h of the onset of symptoms or collapse. **Syncope** was defined as a sudden transient loss of consciousness not requiring electrical cardioversion for recovery. **Ventricular tachycardia** was defined as sustained (>30 s) or non-sustained (≤30 s). The QRS configuration during spontaneous ventricular tachycardia was classified according to the bundle branch block and axis deviation pattern.

**Pathologic data.** **Gross examination.** All hearts were fixed in formalin and examined by the local cardiovascular pathologist (G.T., M.J.D., F.S., F.F.). Macroscopic examination included measurement of heart weight, chamber size and wall thickness, as well as inspection of coronary arteries (origin, course and patency) and valves. The following regions were systematically examined: inflow tract, outflow tract, apex, posterolateral and anterolateral walls of both ventricles and the interventricular septum. The following morphologic changes were addressed: 1) wall thinning; 2) cavity enlargement or aneurysms, or both; 3) myocardial atrophy and fatty replacement; 4) fibrosis; 5) parietal thrombosis; and 6) endocardial fibrosis. The changes were evaluated in terms of severity (mild, moderate, severe), transmural extension (subepicardial to full thickness) and distribution (monofocal, multifocal, diffuse). Extent and distribution of ventricular muscle atrophy were confirmed by wall transillumination.

**ARVC** was defined as **regional** when it was limited to certain RV regions. A **transmural** lesion was defined as one that extended through the entire thickness of the ventricular wall, reaching the endocardium, with or without trabecular involvement. **Subepicardial** and **mediomural** lesions were defined as lesions that affected less than two-thirds of the ventricular wall, sparing the subendocardial portion. **Ventricular aneurysm** was defined as an external bulging or ex vacuo hollow of a thinned ventricular region.

**Histopathologic study.** Full-thickness blocks of myocardium were removed for histologic examination from each region of the right and left ventricles and the septum, in a plan parallel to the long axis of the ventricles. In five cases, a short-axis cut of the whole heart at the mid third, including both ventricles and septum, was also carried out (Fig. 1). Tissue specimens were embedded in paraffin and routinely processed. All myocardial sections (5 to 7 µm thick) were stained with hematoxalin–eosin and azan techniques or hematoxylin–phloxine–safranin O stain. The following morphologic lesions were assessed and graded in the histologic specimens: 1) **myocardial atrophy and fatty replacement** (severity [mild, moderate, severe], transmural extent [subepicardial to full thickness] and distribution [monofocal, multifocal, diffuse]); 2) **myocardial fibrosis** (severity, extent, distribution and type [interstitial or replacement]); 3) **myocyte degeneration** (atrophy, contraction bands, acidophilic degeneration, vacuolization, hypertrophy, and nuclear abnormalities) or **necrosis** (severity, extent and distribution); 4) **interstitial cell infiltrates** (severity, extent, distribution, predominant cell type [lymphocytes, giant cells, neutrophils, eosinophils]) and predominant location [interstitial, perivascular, perimyocyte, perinerve]); and 5) **nerve and intramural vessel abnormalities**.

**Statistical analysis.** Results are expressed as mean value ± SD. The unpaired Student t test was used to determine significance between continuous variables. The chi-square or Fisher test was used to assess the significance of differences between subgroups. A value of p < 0.05 was considered statistically significant.

### Abbreviations and Acronyms

<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ARVC</td>
<td>Arrhythmogenic right ventricular cardiomyopathy/dysplasia</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram, electrocardiographic</td>
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<tr>
<td>LV</td>
<td>Left ventricular</td>
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<td>RV</td>
<td>Right ventricular</td>
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November 15, 1997:1512–20 ARRHYTHMOGENIC RV CARDIOMYOPATHY/DYSPLASIA
The myocardium of the left ventricle and interventricular septum (only fibrosis, predominantly in the anterolateral region of the RV free wall. Diastolic atrophy, mostly consisting of fatty replacement with tiny interstitial paraseptal segments of the LV free wall. Note the transmural myocardial atrophy, mostly consisting of fatty replacement with tiny interstitial paraseptal segments of the LV free wall. The myocardioc of the left ventricle and interventricular septum (only partially visible in the section) is spared. Azan stain ×3, reduced by 30%.

Results

Clinical characteristics. The study group included 42 patients (27 male, 15 female). The age at time of death (or heart transplantation) ranged from 9 to 65 years (mean age 29.6 ± 18). Nine patients had a family history of premature sudden death who died suddenly, without warning symptoms. Short-axis macrohistologic section of the heart at the mid-third, which includes the entire circumference of the RV free wall, the interventricular septum and both anterior and posterior paraseptal segments of the LV free wall. Note the transmural myocardial atrophy, mostly consisting of fatty replacement with tiny interstitial fibrosis, predominantly in the anterolateral region of the RV free wall. The myocardium of the left ventricle and interventricular septum (only partially visible in the section) is spared. Azan stain ×3, reduced by 30%.

A detailed clinical follow-up (from initial evaluation by a cardiologist to death or heart transplantation) was available in 25 patients and ranged from a few months to 25 years (mean 6.35 years). Nine patients had progressive functional limitation, evolving to overt, predominantly right heart failure in eight. In three patients, the clinical course was complicated by embolic cerebrovascular accidents that were fatal in one and led to persistent hemiparesis in two.

Thirty-four patients (83%) died suddenly; the fatal event was exercise related in 16 and occurred during a competitive game in 9. Eight patients were taking antiarrhythmic drugs for ventricular arrhythmias (previous aborted sudden death due to ventricular fibrillation in one, sustained ventricular tachycardia in three, nonsustained ventricular tachycardia in four) at the time of sudden death: amiodarone in four patients (associated with mexiletine in one), sotalol in three and propafenone in one. Pharmacologic therapy had been “empiric” in seven and guided by programmed ventricular stimulation in one. In four patients, fatal cardiac arrest was due to recorded ventricular fibrillation that was preceded by ventricular tachycardia in two. Six hearts were from patients with heart failure refractory to drug therapy who underwent heart transplantation (four patients) or died (two patients). Finally, one patient died of an embolic stroke and another of cerebral malignancy.

A rest 12-lead ECG was available in 28 of 42 patients. Inverted T waves on precordial leads were recorded in 27 patients and showed the following distribution: anteroseptal in 16 (leads V1 and V2 in 7, leads V1 to V3 or lead V4 in 9) (Fig. 2A) and anterolateral (leads V1 to V5 or lead V6) in 10 (with extension to leads L1 and aVL in 4) (Fig. 3A). Other ECG abnormalities included a low voltage QRS complex <1 mV in the peripheral leads in two patients, incomplete right bundle branch block in two, “epsilon waves” on the right precordial leads in two (Fig. 3A) and inverted T waves in the inferior leads (II, III, aVF) in five (Fig. 2A and 3A).

During follow-up, five patients underwent pacemaker implantation for sick sinus syndrome (three patients) or complete atrioventricular block (two patients). Recurrent paroxysmal atrial fibrillation was documented in two patients, both experiencing cerebral embolism.

Ventricular arrhythmias were documented in 27 of 28 patients with available ECG tracings and included spontaneous sustained ventricular tachycardia in 9, nonsustained ventricular tachycardia in 8 and isolated or coupled premature ventricular beats in 10. Two patients had two different sustained ventricular tachycardia morphologies. All types of sustained ventricular tachycardia showed a left bundle branch block pattern, with a superior axis in six patients, and inferior axis in five (Fig. 3B). The ventricular tachycardia rate ranged from 145 to 280 beats/min. Nonsustained ventricular tachycardia ranged from 4 to 15 beats/min (left bundle branch block pattern in five patients, multiform in three). Single and coupled premature ventricular beats were the only documented ventricular arrhythmia in 10 patients (monomorphic with left bundle branch block pattern in 7, two or more morphologies in 3).

Twenty-two patients underwent angiography or cross-sectional echocardiography during life. The underlying cardiomyopathy was not recognized in 7 patients (32%). In the other 15 patients, a diagnosis of RV cardiomyopathy (4 patients) or biventricular cardiomyopathy (11 patients) was made on the basis of global or regional ventricular dysfunction, or both.

Serial echocardiographic examinations (two or more) were performed in 10 patients: progression of structural or functional abnormalities, or both, were observed in eight patients and consisted of worsening of RV function in all, associated with the appearance (two patients) or worsening (five patients) of LV abnormalities.

Pathologic findings. Gross morphologic features. There were 38 necropsy study hearts and 4 transplantation hearts (weight 164 to 780 g, mean 416 ± 140). Global RV dilation was...
seen in all 42 hearts and was mild in 3, moderate in 13 and severe in 26. Aneurysmal dilations were identified in 20 hearts at one or more of the following locations: RV inlet in 13, outlet in 12 (Fig. 3C) and apex in 7. All hearts showed severe and transmural RV muscle loss, with varying degrees of extent and distribution. Atrophy of RV musculature was regional in five cases (sparring inlet in two; apex, apex and inlet, and inlet and outlet in one each) and widespread in the remaining 37. In 15 patients the loss of musculature, although transmural, was homogeneously and completely replaced by fibrofatty tissue and resulted in wall thickness preservation or only slight thinning. In the remaining 27 hearts, the RV free wall disclosed a variable degree of thinning (thickness range 0.5 to 5 mm), with areas so thin as to appear completely devoid of muscle at transillumination (Fig. 2C), and adjacent areas with surviving subendocardial musculature and variable amounts of fibrofatty replacements. Therefore, the RV wall shape appeared irregularly deformed by thinning, scarring and bulging. RV endocardial fibrosis was seen in 14 hearts (diffuse in 8, patchy in 6), and 2 hearts exhibited diffuse epicardial thickening. Mural thrombosis in the RV cavity was found in one instance.

LV involvement was diagnosed at gross examination in 17 hearts. The left ventricle was dilated in all cases (mildly in nine, moderately in four, severely in four). In all hearts, changes in LV musculature consisted of transmural or predominantly subepicardial and mediomural fibrofatty replacement (Fig. 3E), which either affected diffusely both the septum and the free wall (eight cases) or selectively involved some regions, such as the posteroseptal or posterolateral wall, or both (six cases), the anterolateral wall and apex (two cases) and the septum and apex (one case). An anteroseptal LV aneurysm was observed in one instance.

**Histologic findings.** Histologic examination disclosed severe and transmural loss of RV myocardium in all heart specimens (Fig. 1 to 3). According to gross inspection, microscopic lesions diffusely affected the RV free wall in all but five cases. In 15 hearts the RV wall thickness was homogeneously preserved and was almost completely filled with fatty tissue except for a thin subendocardial layer and the trabeculae, which showed surviving myocardium with degenerative changes, atrophy and increased interstitial fibrosis (Fig. 1). The outer epicardial border of wall musculature was often defined by a residual rim of myocardial fibers.

In the other 27 hearts, there were areas of normal thickness adjacent to areas of very severe wall thinning (≤2 mm), which was almost completely devoid of muscle fibers and extensively

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**Figure 2.** Baseline ECG and tissue specimens from a 26-year-old victim of sudden death (group B) with a history of syncope and ventricular tachycardia with a left bundle branch block pattern. Baseline 12-lead ECG with inverted T waves in inferior (L3, aVF) and right precordial (V1, V2) leads (A). Panoramic histologic view of the right ventricular free wall showing transmural fibrofatty replacement (B [azan stain ×3, reduced by 40%]). Panoramic histologic view of the lateral LV free wall disclosing spots of fibrofatty substitution in subepicardial and midmural myocardial areas (C [azan stain ×3, reduced by 43%]). At higher magnification, histologic examination of the affected LV myocardium shows a mononuclear cell inflammatory infiltrate surrounding dying myocytes (D [hematoxin–eosin stain ×240, reduced by 46%]).
replaced by a combination of fibrofatty tissue (Fig. 2B). The epicardial boundary of wall musculature was no longer detectable. Surviving myocardial cells in affected areas disclosed degenerative changes and atrophy.

LV involvement was diagnosed histologically in 32 cases. LV fibrofatty substitution was transmural or predominantly located in the subepicardial and mediomural wall layers in 28 cases (Fig. 2C and 3F); a diffuse increase in interstitial and patchy replacement fibrosis was noted in the other 4 cases. Both the septum and the LV free wall were affected in 23 hearts; 9 hearts disclosed selective free wall (8 hearts) or septal (1 heart) involvement.

Multifocal inflammatory infiltrates were seen in 29 hearts and affected both ventricles and the septum in 25, the RV myocardium only in 3 and the LV myocardium only in 1. Infiltrates consisted of scattered interstitial collections of mononuclear cells, mainly located in the subendocardial region close to necrotic or degenerative myocytes, or both (Fig. 2D). In two cases, the inflammatory process had the features of a focal giant cell myocarditis.

Correlation of results. Table 1 shows the comparison between patients with and without LV involvement with respect to a series of clinical and morphologic variables. Patients were classified into three subgroups according to the presence and severity of LV involvement: 1) group A = 10 patients with isolated RV involvement (no LV lesions); 2) group B = 15 patients with histologic LV involvement only; 3) group C = 17 patients with both histologic and macroscopic LV involvement.

Patients in group C were significantly older than patients in groups A and B (39 ± 15 years vs. 20 ± 8.8 and 25 ± 9.7 years, respectively), had longer clinical follow-up (9.3 ± 7.3 years vs. 1.2 ± 2.1 and 3.4 ± 2.2 years, respectively), developed heart failure significantly more often (47% vs. 0% and 0%, respectively),
tively) and had an echocardiographic diagnosis of cardiomyopathy (100% vs. 45% and 0, respectively). Patients in groups B and C had warning symptoms significantly more often (80% and 87%, respectively, vs. 30%) and clinical ventricular arrhythmias (73% and 82%, respectively, vs. 20%) than patients in group A. In patients with LV involvement only, inverted T waves on the lateral precordial leads (V5 and V6) were recorded significantly more often in group C patients than group B patients (71% vs. 10%). With regard to morphologic variables, hearts from group C patients weighed more than those from group A and B patients (500 ± 150 g vs. 328 ± 40 and 380 ± 95 g, respectively); hearts from group B and C patients had RV thinning (≤2 mm) (87% and 71%, respectively, vs. 20%) and inflammatory infiltrates (73% and 88%, respectively vs. 30%) significantly more often than those from group A patients. There was no statistically significant difference between the three groups with regard to family history for sudden death or ARVC, athletic activity, occurrence of syncope, right precordial T wave inversion, pacemaker implantation and presence of RV aneurysms.

**Discussion**

ARVC is a heart muscle disease that is characterized pathologically by RV myocardial atrophy and fibrofatty replacement (1–5). Although initially considered to be strictly confined to the right ventricle, there is growing clinical evidence that over time, the left ventricle shares RV cardiomyopathic changes (19–28). Long-term follow-up data from clinical studies indicate that some patients with typical segmental RV disease and a normal left ventricle at initial evaluation
progressevely develop more diffuse RV involvement and LV abnormalities with heart failure (21,22,24). This finding led the World Health Organization/International Society and Federation of Cardiology Task Force to define ARVC as a disease of the myocardium “characterized by progressive fibrofatty replacement of RV myocardium, initially with typical regional and later global RV and some LV involvement” (29). Recognition of patients with ARVC with biventricular involvement may be difficult because they may resemble patients with advanced dilated cardiomyopathy (22,24,27,28,30).

The present study reevaluated the anatomic and clinical profile of ARVC, with special reference to disease progression and LV involvement, by studying a large number of whole hearts with distinctive RV myopathic changes and correlating morphologic findings with clinical findings. The study revealed that ARVC is a progressive heart muscle disease that may present with the following clinicopathologic patterns: “silent” myopathic abnormalities localized to the right ventricle in asymptomatic victims of sudden death; “overt” disease characterized by segmental or global RV structural changes, often associated with only histologic evidence of LV involvement and underlying symptomatic ventricular arrhythmias; “end-stage” biventricular cardiomyopathy mimicking dilated cardiomyopathy, which leads to progressive heart failure and may require heart transplantation.

LV involvement. Previous reports (19–27) have suggested that the left ventricle may be involved in ARVC, with global or segmental disease, mostly located in the apical and inferoposterior regions. In the present study, macroscopic or histologic LV involvement, or both, was found in 76% of the hearts analyzed, thus confirming that ARVC affects the left ventricle in the majority of cases. LV changes usually affected both the septum and LV free wall, either diffusely or, more often, regionally, with a predilection for the posteroseptal and posterolateral areas. Lesions consisted of large areas of transmural or subepicardial, or both, and mediomural fibrofatty replacement of LV musculature. Patients with histologic LV changes disclosed patchy subepicardial and mediomural fibroadipous substitution or a diffuse increase in interstitial fibrosis. The waveform of the lesion appeared to extend from the outer to the inner layer of the LV wall, similar to the pattern of involvement that has been recognized in the RV free wall. It is noteworthy that subepicardial myocardial lesions of the LV wall are rare in other cardiac diseases. In fact, in a study of >5,500 hearts, Shirani and Roberts (31), reported subepicardial myocardial lesions in only 22, 6 of which showed the presence of coronary artery disease.

Hearts with LV abnormalities weighed more and exhibited RV as well as LV myocardial inflammatory infiltrates. Although it is not clear whether inflammation in ARVC is a primary event or a reaction to spontaneous necrosis (32), inflammatory infiltrates are an histopathologic marker of an ongoing myocardial damage that suggests a progressing myocardial disease (28,32,33). The observation of giant cell myocarditis in two patients does not permit any etiopathogenetic speculation because multinuclear giant cells have been reported (34) to accompany various types of inflammatory response of unknown etiology and in diverse clinical settings. In addition, LV involvement was age dependent, was more common in patients with longstanding clinical history and progressed during serial echocardiographic examinations in some patients. All these findings strongly suggest that LV involvement is the result of ARVC progression. If the LV involvement is due to the same disease process as that for the RV lesions or is mediated by different or superimposed pathobiologic mechanisms, or both, remains to be established. Apoptosis has recently been shown (35–38) to be a mode of myocyte death in ARVC and might provide a unifying explanation for progressive biventricular myocardial loss.

The high prevalence and the distinctive “mural” distribution of LV changes are in agreement with the recent study of Wichter et al. (39), in which MIBI scintigraphy provided evidence for a structural or functional sympathetic denervation in regions of LV myocardium adjacent to the right ventricle in patients with ARVC. Because sympathetic nerve trunks course in the subepicardium (40), they may be involved early in the disease progression. It would be interesting to establish whether apoptosis may involve ganglia and nerves as well.

The involvement of the conduction system in the present study appeared as a late complication in the natural history of the disease. Severe bradyarrhythmias, such as sinus sick syn-
ARVC usually has a more benign clinical course than that reported in the present study, which addressed only patients who died and patients undergoing heart transplantation, with the most striking morphologic and clinical features of the disease. Nevertheless, the primary aim of the present study was to redefine the anatomic and clinical profile of ARVC, with special reference to LV involvement and progression, in patients with the disease proved at autopsy.

The present study did not address atrial myocardial pathology, although fatty infiltration even of atrial myocardium has been occasionally observed in ARVC and may account for sinus node dysfunction and other atrial arrhythmias.

Conclusions. ARVC is a progressive heart muscle disease that may present clinically different stages. The tendency to progress and to involve the left ventricle accounts for a wide range of clinical and pathologic manifestations. The spectrum ranges from concealed RV myopathic changes detected at autopsy in previously asymptomatic young victims of sudden death to biventricular cardiomyopathy with severe pump failure.

References


