Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy

Naser M. Ammash, MD; James B. Seward, MD; Kent R. Bailey, PhD; William D. Edwards, MD; A. Jamil Tajik, MD

Background—Idiopathic restrictive cardiomyopathy is a poorly recognized entity of unknown cause characterized by nondilated, nonhypertrophied ventricles with diastolic dysfunction resulting in dilated atria and variable systolic function.

Methods and Results—Between 1979 and 1996, 94 patients (61% women) 10 to 90 years old (mean, 64 years) met strict morphological echocardiographic criteria for idiopathic restrictive cardiomyopathy, mainly dilated atria with nonhypertrophied, nondilated ventricles. None had known infiltrative disease, hypertension of >5 years’ duration, or cardiac or systemic conditions associated with restrictive filling. Nineteen percent were in NYHA class I, 53% in class II, and 28% in class III or IV. Atrial fibrillation was noted in 74% of patients and systolic dysfunction in 16%. Follow-up (mean, 68 months) was complete for 93 patients (99%). At follow-up, 47 patients (50%) had died, 32 (68%) of cardiovascular causes. Four had heart transplantation. The death rate compared with actuarial statistics was significantly higher than expected (P<0.0001). Kaplan-Meier 5-year survival was 64%, compared with expected survival of 85%. Multivariate analysis using proportional hazards showed that the risk of death approximately doubles with male sex (hazard ratio [HR] = 2.1), left atrial dimension >60 mm (HR=2.3), age >70 years (HR=2.0), and each increment of NYHA class (HR=2.0).

Conclusions—Idiopathic restrictive cardiomyopathy or nondilated, nonhypertrophic ventricles with marked biatrial dilatation, as defined morphologically by echocardiography, affects predominantly elderly patients but can occur in any age group. Patients present with systemic and pulmonary venous congestion and atrial fibrillation and have a poor prognosis, particularly men >70 years old with higher NYHA class and left atrial dimension >60 mm. (Circulation. 2000;101:2490-2496.)

Key Words: cardiomyopathy ■ echocardiography ■ prognosis ■ survival

Primary cardiomyopathies have characteristic features and are classified functionally into 3 major categories: dilated, hypertrophic, and restrictive, depending on their disorders of structure and function.1–3 In 1996, the World Health Organization (WHO)/International Society and Federation of Cardiology Task Force added 2 more classes: arrhythmogenic right ventricular cardiomyopathy and unclassified cardiomyopathies.4 The description of dilated and hypertrophic cardiomyopathies is based primarily on morphological criteria, as their names imply. However, restrictive cardiomyopathy (RCM) is a primary abnormality of diastolic function caused by derangement in the dynamics of ventricular filling, resulting in an increase in ventricular end-diastolic pressures and dilated atria. Systolic function is preserved in most cases, depending on the underlying cause.

Secondary RCM can develop at a late stage in hypertrophic, dilated, valvular, hypertensive, and ischemic heart disease or a specific heart muscle disease such as amyloidosis.5–10 However, idiopathic, or primary, RCM occurs in the absence of any such identifiable cause and is thought to be uncommon. A large-cohort follow-up study of primary RCM is unavailable. Using very strict selection criteria, we studied the clinical profile and echocardiographic and morphological features of this disease and analyzed outcome and determinants of survival.

Methods

This is a retrospective cohort study of patients evaluated at the Mayo Clinic between 1979 and 1996 who had an echocardiographic examination demonstrating the characteristic morphological features of (1) biatrial enlargement, (2) nondilated ventricles, and (3) normal ventricular wall thickness. Patients were excluded if they had any known or documented ischemic heart disease (previous infarction, revascularization, >70% diameter coronary stenosis); treated hypertension for >5 years (arbitrary cutoff to exclude secondary restriction); organic valvular, congenital, or pericardial diseases; carcinoid syndrome; connective tissue disease; amyloidosis; hemochromatosis; eosinophilic syndrome; malignancy; radiation; or history of alcohol abuse or intake of cardiotoxic drugs. A detailed medical records review of patients who met the inclusion criteria was...
undertaken with particular attention to (1) demographics; (2) clinical presentation at the time of the initial diagnosis; (3) ECG; (4) chest radiograph; (5) CT scan of the chest; (6) echocardiogram, including spectral and color flow Doppler examination (studies performed after 1985) and atrial volume determination, which was calculated according to the methods of Ren et al and Bommer et al; and (7) cardiac catheterization, including myocardial biopsy findings if performed.

Follow-up evaluation by visit, telephone, or letter was attempted for all patients. If the patient had died, an attempt was made to identify the cause (cardiac, sudden death, stroke, infection, noncardiac, indeterminant).

Statistical Analysis
Data are summarized by mean and SD or frequency percents. Group differences were assessed by $\chi^2$ tests for discrete variables and $t$ tests for continuous variables. Survival follow-up data were analyzed by Kaplan-Meier survival curve estimation and by univariate and multivariate Cox proportional hazards regression analysis. Significance was judged at the 2-sided 0.05 level.

Results
Clinical Profile
The study cohort consisted of 94 patients (57 women, 61%). At the time of initial evaluation, the age range was from 10 to 90 years (mean, 64 years; median, 68 years). As shown in Figure 1, 72% of patients were ≥60 years old. The clinical profile of the patients is summarized in Table 1. The most common symptoms were dyspnea (71 patients) and edema (43 patients). Twenty-one patients had atypical chest pain. Most patients (72%) were in NYHA functional class I or II, and only 1 was in class IV. Eighteen patients had a history of treated hypertension for , 5 years, 11 had diabetes mellitus, 35 were previous smokers, and 9 were current smokers; only 2 had a family history of cardiomyopathy. On examination, the most common signs were jugular venous distension (43 patients), Twenty-one patients had atypical chest pain. Most patients (72%) were in NYHA functional class I or II, and only 1 was in class IV. Eighteen patients had a history of treated hypertension for <5 years, 11 had diabetes mellitus, 35 were previous smokers, and 9 were current smokers; only 2 had a family history of cardiomyopathy. On examination, the most common signs were jugular venous distension (43 patients, 52%), systolic murmur (46 patients, 49%), and lower-extremity edema (14 patients). Constrictive pericarditis was clinically suspected in 40 patients and was excluded by additional tests, including CT in 19, cardiac catheterization in 18, and thoracotomy in 3.

Electrocardiography
The 12-lead ECG at the time of the initial diagnosis was reviewed in all patients and demonstrated atrial fibrillation in

70 patients (74%), sinus rhythm in 20 (21%), and paced rhythm in 4. Of those in sinus rhythm, 4 had a history of paroxysmal atrial fibrillation. None of the patients had left ventricular hypertrophy or a low QRS voltage. Eighteen patients (19%) had an intraventricular conduction delay. Nonspecific ST-T–wave abnormalities were noted in 75 patients, premature ventricular beats in 13, and premature atrial beats in 5. Two patients had a normal ECG.

Chest Radiography
A chest radiograph was available in all 94 patients. Cardiomegaly, defined by a cardiothoracic ratio >55%, was the predominant abnormality on chest radiography and was noted in 69 patients (73%). Other findings included pulmonary venous congestion in 45 patients (48%), interstitial edema in 11, and pleural effusion in 17. Pericardial calcification was not noted in any patient. CT of the heart was performed in 19 patients because of clinically suspected constrictive pericarditis; none had pericardial calcification or thickening. Seventeen patients had a normal chest radiograph.

Echocardiography
The echocardiographic morphological features typical of RCM are shown in Figure 2. These include biatrial enlargement, nondilated ventricles, and normal wall thickness. These features were present in all 94 patients. The echocardiographic findings in our study cohort are summarized in Table 2. Measurements of left atrial diameter were obtained in 85 patients (90%) and averaged at 50 mm. In the 9 other patients, the atria were visually estimated to be enlarged. Left atrial volume was calculated in 44 patients, and the average was 142 mL. Average left ventricular end-diastolic diameter was 47 mm. Left ventricular ejection fraction was assessed quantitatively, by shortening fraction or volumetric method, in 86
Table 2. Echocardiographic and Catheterization Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>40–82</td>
<td>50 (9)</td>
</tr>
<tr>
<td>LA volume, mL</td>
<td>62–476</td>
<td>142 (76)</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>30–55</td>
<td>47 (6)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>18–80</td>
<td>59 (13)</td>
</tr>
<tr>
<td><strong>Catheterization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA pressure, mm Hg</td>
<td>4–39</td>
<td>15 (8)</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>4–37</td>
<td>17 (7)</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>7–40</td>
<td>23 (7)</td>
</tr>
<tr>
<td>PASP, mm Hg</td>
<td>24–75</td>
<td>47 (15)</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>12–31</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Cardiac index, L · min⁻¹ · m⁻²</td>
<td>1–4.7</td>
<td>2.4 (1)</td>
</tr>
</tbody>
</table>

LA indicates left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RA, right atrial; RVEDP, right ventricular end-diastolic pressure; LVEDP, left ventricular end-diastolic pressure; PASP, pulmonary artery systolic pressure; and PCWP, pulmonary capillary wedge pressure.

Cardiac Catheterization

Cardiac catheterization was performed in 38 patients, including right heart catheterization in 30. A left ventricular angiogram was performed in 28 patients (30%). It calculated an ejection fraction ranging from 22% to 78%. Twenty-four of these patients also had a quantitative echocardiographic assessment of ventricular function. The hemodynamic findings are summarized in Table 2. The mean right atrial pressure was increased (>8 mm Hg) in 24 of the 30 patients (80%). Similarly, right ventricular end-diastolic pressure was ≥10 mm Hg in 27 of the 30 patients. Pulmonary capillary wedge pressure was ≥18 mm Hg in 17 patients. Left ventricular end-diastolic pressure averaged 23 ± 7 mm Hg. The cardiac index was measured by use of dye dilution curve or thermodilution and ranged from 1 to 4.7 L · min⁻¹ · m⁻². End-diastolic equalization of pressure was noted in 42% of patients and the square root sign in 43%. Coronary angiography was performed in 29 patients and demonstrated luminal irregularities in 17. Twelve patients had mild coronary artery disease with <70% diameter stenosis. None had diabetes mellitus. Eleven of these patients (92%) had no regional wall abnormalities. The remaining patient had severe global dysfunction (EF < 19%) that could not be explained solely on the basis of 1-vessel coronary artery disease. The myocardial biopsy performed confirmed the diagnosis of cardiomyopathy.

Myocardial Biopsy

Endomyocardial biopsy was performed percutaneously in 33 patients, by thoracotomy in 3, and at autopsy in 1 (Figure 3). Biopsy specimens obtained from 30 patients (81%) demonstrated interstitial fibrosis, predominantly pericellular, that was moderate to severe in 17. Perivascular fibrosis was noted in only 5 patients. Thirty-two patients (86%) had myocyte hypertrophy, which was mild to moderate in severity in 30. Myocyte attenuation was noted in 8 patients (27%) and degeneration in 10. Microscopic examination of the endocardium demonstrated endocardial fibrosis in 15 patients (45%), with no inflammatory changes. None of the biopsy specimens demonstrated amyloid or iron deposition, caseating granulomas, eosinophilic or lymphocytic infiltrates, or any interstitial inflammatory changes.

Follow-Up

Follow-up was complete for 93 patients (99%), with a mean duration of 68 months (range, 1 to 128 months). Eighteen patients (19%) returned to the clinic; another 17 answered a questionnaire by mail. For the remaining 58 patients, follow-up information was obtained by phone with the patient if alive and with next of kin or primary physician if deceased. Forty-seven patients (50%) had died. Death was attributed to congestive heart failure in 22 patients, sudden death in 8, cardiac arrhythmias in 5, and cerebrovascular accident in 2. Overall, cardiovascular system–related death was observed in 32 patients (68%). The 15 other patients (32%) died of newly diagnosed cancer (6 patients), infection (6 patients), motor vehicle accident (1 patient), or indeterminant cause (2 patients). Postmortem examination was performed in only 2 patients and did not demonstrate infiltrative cardiomyopathy, such as amyloidosis.
Among the 46 survivors, 28% were in NYHA class I, 46% in class II, and 17% in class III. The 4 other patients (9%) had cardiac transplantation. The overall observed survival in the study cohort was significantly reduced compared with expected age- and sex-matched survival data (1-sample log-rank \( P < 0.001 \)) (Figure 4). The 5-year observed survival was 64%, compared with 85%, and 10-year survival was 37%, compared with 70%. Univariate analysis demonstrated that survival was not significantly related to age, duration of symptoms, atrial fibrillation, cardiomegaly, systolic dysfunction, pulmonary artery pressure, left ventricular end-diastolic pressure, biopsy findings, or medications. However, survival was significantly adversely related to male sex \( (P = 0.033) \), NYHA functional class \( (P = 0.007) \), pulmonary venous congestion on chest radiography \( (P = 0.026) \), pulmonary wedge pressure \( > 18 \text{ mm Hg (P = 0.032)} \), and left atrial diameter \( > 60 \text{ mm (P = 0.027)} \) (Figure 5). Multivariate analysis demonstrated that the risk of death was significantly independently associated with male sex (hazard ratio, 2.1), age >70 years (hazard ratio, 2.0), each increment in NYHA class (hazard ratio, 2.0), and left atrial diameter >60 mm (hazard ratio, 2.3).

**Figure 4.** Kaplan-Meier survival curve for observed survival in study cohort compared with expected survival in age- and sex-matched group.

**Discussion**

Diseases of heart muscle, or cardiomyopathies, with secondary systolic or diastolic heart failure contribute significantly to cardiovascular morbidity and mortality. Definition of the 2 most common cardiomyopathies is based on the morphology of the left ventricle, that is, either dilated with normal wall thickness and depressed ventricular function (dilated cardiomyopathy) or hypertrophied walls with small ventricular cavity and hyperdynamic function (hypertrophic cardiomyopathy). In contradistinction, the definition of RCM, as proposed by WHO, is based on altered hemodynamics (restrictive filling) and not an abnormal morphology.\(^4\) We propose a morphological definition of idiopathic RCM based on echocardiographic features demonstrating nondilated, nonhypertrophied ventricles, with marked biastral enlargement in the absence of ischemic, valvular, hypertensive, congenital, inflammatory, or infiltrative heart diseases. The dilated atria are the consequence of increased filling pressures (restrictive hemodynamics). Idiopathic RCM is a rare and poorly characterized entity that should not be confused or equated with other diseases resulting in restrictive hemodynamics. The latter can occur with many advanced primary or secondary cardiac diseases, such as ischemic, valvular, or infiltrative conditions such as amyloidosis.\(^5,6\) Idiopathic RCM has been reported in small series of 9, 4, and 5 patients.\(^5,9,13\) However, these series included patients with hypertension, coronary disease, neurofibromatosis, and echocardiographic or autopsy findings of ventricular hypertrophy or enlargement. Our study, to the best of our knowledge, has excluded patients in whom RCM could have been secondary to other disease states.

**Clinical Profile**

Idiopathic RCM is more common in older women than men (F:M ratio, 1.5:1). Its clinical features, often indistinguishable from those of constrictive pericarditis, are elevated systemic and pulmonary venous pressures (congestive heart failure), with atrial fibrillation being very common (74%). In all but
mild cases of RCM, jugular venous pressure is increased. The left ventricular impulse is usually normal and palpable. A third heart sound is not unusual because of rapid ventricular filling. Systolic murmurs of mitral and tricuspid regurgitation are also common. Other physical findings, especially in an advanced stage, include pulmonary congestion, hepatomegaly, ascites, and edema.

**Diagnostic Approach**

Patients presenting with congestive heart failure often undergo a series of diagnostic evaluations to determine the underlying cause. In patients with idiopathic RCM, the ECG is invariably abnormal but is nonspecific. The predominant rhythm is atrial fibrillation with premature beats and conduction delay. In contradistinction to amyloid heart disease, which is the most commonly studied entity as a prototype of RCM, the QRS voltage is not low but rather normal in idiopathic RCM. The chest radiograph can be near normal in the early stage of idiopathic RCM. However, in symptomatic patients, it commonly shows the radiographic appearance of moderate-to-marked generalized cardiomegaly due to biatrial enlargement with pulmonary venous congestion and pleural effusions, as demonstrated in our study and reported by others. Pericardial calcification, if noted, should raise suspicion of constrictive pericarditis. Ultrafast CT, MRI, catheterization, and echocardiography are reliable diagnostic techniques for identifying pericardial constriction.

Echocardiography is the method of choice for assessing the morphological and functional characteristics of cardiomyopathies and therefore is the procedure of choice in patients presenting with heart failure. Idiopathic RCM is one of the causes of diastolic heart failure. The diagnosis of idiopathic RCM is characterized morphologically by nondilated, nonhypertrophied (normal wall thickness) ventricles with biatrial enlargement (Figure 2), with the latter reflecting the increased ventricular and atrial filling pressures. Left ventricular systolic function is preserved in most patients (84%), and mild-to-moderate tricuspid and mitral valve regurgitation is common. The typical restrictive filling pattern can be recognized by increased mitral E velocity, increased ratio of mitral early to late filling (E/A ratio >2), and shortened deceleration time (typically <150 ms). These were noted in the majority of our patients who were in sinus rhythm. An important limitation to Doppler evaluation of diastolic function is that the filling variables are dependent on heart rate, PR interval, loading condition, age, presence of valvular regurgitation, atrial fibrillation, breathing pattern (apnea), and location of sample volume. The interplay of these factors should be considered in interpreting these variables. Finally, as demonstrated by Cetta et al in children with idiopathic RCM, right ventricular systolic pressure was increased in 87% of patients in whom it was measured, reflecting increased filling pressure.

Patients with suspected idiopathic RCM may require a thorough hemodynamic evaluation with cardiac catheterization to confirm the diagnosis and to exclude constrictive pericarditis and infiltrative myocardial disease such as amyloidosis. Our study demonstrated that an elevation of end-diastolic pressures was the major finding. These hemodynamic findings are identical to those of constrictive pericarditis. Typically, however, in RCM, unlike constrictive pericarditis, the right ventricular end-diastolic pressure is

![Image](http://circ.ahajournals.org/)

**Figure 5.** Survival curves in relation to sex (A), NYHA functional class (I to III; B), pulmonary venous congestion (C), and left atrial dimension >60 mm (D).

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*Note: The image contains graphs with survival curves and patient outcomes, which are not translatable into plain text.*
5 mm Hg lower than that of the left ventricle because of unequal involvement and compliance of the 2 chambers. Intervention such as exercise, volume infusion, and cardioactive drugs to separate left from right ventricular pressure can be of limited value, because negative results cannot entirely exclude RCM or confirm constrictive pericarditis. When the latter is clinically suspected, CT of the chest would be indicated. This was performed in 19 patients. Furthermore, myocardial biopsy should be considered in patients with a suspected secondary form of restrictive heart muscle disease, such as amyloidosis, hemochromatosis, sarcoidosis, or hypereosinophilic syndrome. This is especially true in the presence of suggestive findings, such as increased wall thickness on echocardiography, low voltage on ECG, high eosinophil count, or the presence of systemic manifestations of the disease. None of these were present in our patient population. In idiopathic RCM, as demonstrated in our study, myocardial biopsy typically demonstrates patchy endocardial and interstitial fibrosis with compensatory myofibril hypertrophy without myofiber disarray, or findings suggestive of a specific infiltrative heart muscle disease.

**Outcome**

Little is known about the prognosis of true idiopathic RCM, because most published reports have included patients with known chronic hypertension, coronary artery disease, and even ventricular enlargement and hypertrophy, and as a result, their outcome was substantially different from that observed in this study. In this study, we have attempted, to the best of our ability, to exclude patients with a possible secondary form of RCM by adhering to very strict inclusion and exclusion criteria. Recently, Cetta et al. and Lewis reported on the clinical course in small series of children with idiopathic RCM. They noted a median survival of only 1.0 to 1.4 years. Similarly, Denfield et al. noted that the actuarial 2-year survival rate for children with RCM was <50%. Our study, compared with those published reports, included patients of all ages. The observed overall survival was significantly lower than that expected for an age- and sex-matched group (P < 0.001). The 5-year overall survival was 64% versus the expected 85%, and the observed 10-year survival was 37% versus the expected 70% (Figure 4). Survival by multivariate analysis was related adversely to male sex, age >70 years, each increment in NYHA functional class, and left atrial diameter. These findings suggest that idiopathic RCM might have a protracted course in the early phase of the disease, when patients are younger and symptoms and atrial enlargement are mild. However, older patients, particularly men, with increasing symptoms and signs of systemic and pulmonary venous congestion and echocardiographic evidence of significant enlargement of the left atrium have the worst prognosis.

Idiopathic RCM may be a biochemical abnormality of the energy-dependent rapid filling phase of cardiac relaxation, a process that requires pumping calcium out of the cytosol, resulting in decreased diastolic wall tension. To date, treatment is not well defined and is directed at reducing pulmonary and systemic congestion by carefully decreasing filling pressure with diuretics, controlling heart rate to allow adequate filling time, maintaining atrial contraction, correcting atrioventricular conduction disturbance with permanent pacing if needed, and avoiding anemia, nutritional deficiency, calcium overload, and electrolyte imbalance. In addition, patients in atrial fibrillation should be considered for chronic anticoagulation to decrease the risk of thromboembolism. Experience with cardiac transplantation in RCM is limited, but transplantation is potentially beneficial. Four of our patients eventually underwent cardiac transplantation.

**Limitations**

This retrospective study of a rare disease required data collection over 17 years, during which 19% of patients returned for follow-up and a large proportion died of cardiovascular causes. A very small group had gross and histological examination of the heart. In addition, as a result of the retrospective design of this study, not all patients had all the diagnostic tests that can be considered at the present time, such as Doppler tissue imaging, gated single photon emission CT scintigrams, intravascular ultrasound, MRI, and electron beam CT. However, all had comprehensive 2D echocardiographic examination, which showed the typical features of RCM. Cardiac catheterization and endomyocardial biopsy were done only when considered clinically justified by the attending consultant cardiologist; thus, an invasive hemodynamic examination was performed in 38 patients and biopsy in 33. These limitations are inherent to the retrospective design of the study and are fully acknowledged.

**Conclusions**

The presence of dilated atria with nonhypertrophied, nondilated ventricles in patients with congestive heart failure should be more commonly recognized as a separate disease entity and should raise the suspicion of RCM, idiopathic or secondary. This study describes the clinical, echocardiographic, and hemodynamic features of patients with the morphological characteristics of idiopathic RCM. Keeping in concert with the WHO classification of dilated and hypertrophic cardiomyopathies based on morphology, it is now proposed that RCM can also be similarly diagnosed on the basis of the characteristic morphology (dilated atria) with nonhypertrophied, nondilated ventricles. Although these features of RCM are nonspecific, our study clearly demonstrates that the mere presence of dilated atria, in the absence of ventricular enlargement, hypertrophy, and even systolic dysfunction, is associated with adverse outcome. The pathophysiological alterations of the endomyocardium that lead to elevated filling pressures, thereby causing atrial enlargement, are not fully understood and are the subject of much ongoing research.

**References**

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