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Clinical features of idiopathic restrictive cardiomyopathy
A retrospective multicenter cohort study over 2 decades

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Abstract

Idiopathic restrictive cardiomyopathy (RCMP) has not been fully understood because this disease is difficult to diagnose. The present study aimed to assess the clinical profile and outcome of idiopathic RCMP from a multicenter cohort.

This investigation is a retrospective study of consecutive patients with idiopathic RCMP at 10 centers in Korea between 1990 and 2010. We evaluated the clinical characteristics of the patients and prognostic factors associated with mortality using multivariate Cox proportional hazards regression analyses.

The study included 53 patients (26 men, 49.1%). During a median follow-up of 1.7 years, 17 patients (32.1%) died and 5 patients (9.4%) received a heart transplant. The 5-year survival rate of the overall patients was 64.4% $\pm$ 7.8%. In multivariable analyses, the predictors of mortality were tricuspid regurgitation (TR) $\geq$ moderate (hazard ratio [HR] 32.55, $P < .001$) and left ventricular end-diastolic diameter (LVEDD) (HR 0.85, $P < .001$).

Idiopathic RCMP showed unfavorable prognosis. Advanced TR and lower LVEDD are independent adverse predictors of mortality in patients with idiopathic RCMP.

Abbreviations: EDP = end-diastolic pressure, EF = ejection fraction, HR = hazard ratio, LA = left atrium, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, NYHA Fc = New York Heart Association functional class, RCMP = restrictive cardiomyopathy, RV = right ventricle, RVEDP = right ventricle end-diastolic pressure, TR = tricuspid regurgitation.

Keywords: idiopathic restrictive cardiomyopathy, outcome, risk factor

1. Introduction

Restrictive cardiomyopathy (RCMP) is a rare disease category characterized by increased stiffness of the ventricles in the

presence of normal diastolic volume and normal ventricular wall thickness.[1] Especially, idiopathic RCMP is diagnosed in the absence of any identifiable causes such as storage, systemic, and inflammatory disease. This cardiomyopathy has been of great concern for physicians because of poor prognosis and no effective treatment. However, idiopathic RCMP had not been fully understood because it is the least common cardiomyopathy.[2,3] Furthermore, this disease is difficult to diagnose owing to its broad diagnostic criteria based on functional and morphological character. There is the possibility of any unidentifiable etiologies at diagnosis or the risk of misdiagnosis from some similarity with hypertrophic or dilated cardiomyopathy.

Little is known about the clinical features of idiopathic RCMP. Ammash et al[4] reported idiopathic RCMP in 97 adult patients across ethnic groups. However, their study was limited by the single-center nature. Moreover, with recent developments in genetic testing, idiopathic RCMP may be affected by genetic factors suggesting the racial differences in clinical characteristics.[5,6] Therefore, we aimed to assess the clinical features and outcomes of idiopathic RCMP from a Korean multicenter cohort.

2. Methods

2.1. Subjects/populations

This was a retrospective study of patients evaluated at 10 centers in Korea between 1990 and 2010 whose echocardiographic examination demonstrated the characteristic features of restrictive ventricular physiology, normal or reduced end-diastolic

volumes, and normal ventricular wall thickness. Patients were excluded if they had any ischemic heart, organic valvular, congenital, or pericardial disease. Patients with known infiltrative, metabolic, and syndromic causes of RCMP were also excluded. However, impairment of left ventricular (LV) ejection fraction (EF) was not an exclusion criterion. The clinical presentation of RCMP shows wide spectrum including not only diastolic dysfunction but also systolic dysfunction as an integral part of specific pathologies.[7] Patients with RCMP can often exhibit LV systolic dysfunction in the end-stage phase of the disease. Medical records of patients who met the inclusion criteria were reviewed. The echocardiography study date of these patients was defined as the initial encounter time, and follow-up was conducted through clinic visit or via telephone. The present study was approved by the review board of the Asan Medical Center (ID: 2015-0958). All data were retrospective observational cases of patients who received standard diagnostic approach and therapy; therefore, informed consent for each patient was not given.

2.2. Statistical analysis

Continuous baseline characteristics and echocardiographic findings are presented as mean±standard deviation, and categorical variables are summarized as frequency percentages. Survival follow-up data were analyzed with Kaplan–Meier survival curve estimation, and with univariate and multivariate Cox proportional hazards regression analyses. Variables with a probability value of ≤0.20 in univariate analyses were candidates for multivariable Cox proportional hazards models. Statistical analyses were performed with SPSS Statistics version 20 (IBM Corporation, Armonk, NY).

3. Results

3.1. Baseline characteristics

The study included 53 patients (26 men, 49.1%). The mean follow-up duration was 3.5±4.4 years, and the median follow-up was 1.7 years.

The mean patient age was 53.2 years, and dyspnea of New York Heart Association functional class (NYHA Fc) III or higher was found in 47.2%. Signs such as pulmonary congestion and pleural effusion were also found in 50.3%. On electrocardiogram, atrioventricular block was observed in 5 patients (9.4%), and atrial fibrillation was observed in 14 patients (26.4%). The clinical profile of the patients is summarized in Table 1.

3.2. Echocardiography

The overall echocardiography results confirmed the typical findings of RCMP. The echocardiographic characteristics are summarized in Table 1. The average left atrial (LA) diameter was 49.0 mm. The average left ventricular end-diastolic diameter (LVEDD) was 46.3 mm. The EF averaged 51%. Transmitral valve Doppler was performed. The average E/A was high as 3.7 in 39 patients who showed sinus rhythm, and the average deceleration time was 172.5 ms. Moderate or more mitral regurgitation was defined as jet area ≥5 cm^2, proximal isovelocity surface area radius ≥5 mm, and Effective Regurgitant Orifice ≥0.20 cm^2. And moderate or more tricuspid regurgitation (TR) was defined as jet area ≥5 cm^2 and proximal isovelocity surface area radius ≥6 mm.[8] Only small proportion of subjects presented with moderate or more mitral regurgitation or TR.

Baseline characteristics, clinical profile, and echocardiographic findings.

Variable, unit	Total (N = 53)
Age, y	53.2 ± 20.1
Sex (male)	26 (49.1)
Hypertension	15 (28.3)
Diabetes	14 (26.4)
Atrial fibrillation	14 (26.4)
History of VT/VF	2 (3.8)
RBBB	5 (9.4)
LBBB	5 (9.4)
Atrioventricular block	5 (9.4)
NYHA Fc I	6 (11.3)
II	22 (41.5)
III	15 (28.3)
IV	10 (18.9)
Pulmonary congestion	27 (50.9)
Pleural effusion	27 (50.9)
LVEDD, mm	46.3 ± 7.7
LA diameter, mm	49.0 ± 8.4
LVEF, %	51.0 ± 13.5
E, cm/s	87.9 ± 42.1
A, cm/s	46.0 ± 32.8
E/A	3.70 ± 5.96
DT, ms	172.5 ± 83.5
MR (≥moderate)	2 (3.8)
TR (≥moderate)	4 (7.5)
TR Vmax, m/s	3.3 ± .5
RV dysfunction	4 (7.5)

A, peak velocity of the late filling wave due to atrial contraction; E, peak mitral flow velocity of the early rapid filling wave. DT = deceleration time, EF = ejection fraction, LA = left atrial, LBBB = left bundle branch block, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, NYHA Fc = New York Heart Association functional class, RBBB = right bundle branch block, RV = right ventricular, TR = tricuspid regurgitation, VF = ventricular fibrillation, VT = ventricular tachycardia.

3.3. Cardiac catheterization

Cardiac catheterization was performed in 5 of 53 (9.4%) patients. The LV end-diastolic pressure (EDP) was 24.0 ± 7.2 mm Hg, and the right ventricular (RV) EDP was 10.4 ± 8.1 mm Hg. The pulmonary capillary wedge pressure was 23.5 ± 2.1 mm Hg, and the pulmonary artery systolic pressure was 39.2 ± 8.8 mm Hg.

3.4. Myocardial biopsy

Percutaneous RV endomyocardial biopsy was performed in 22 patients (41.5%). Histological findings confirmed interstitial fibrosis and edema in 11 patients (50.0%), and myocyte hypertrophy in 10 patients. Myocyte irregular branching was noted in 3 and degeneration was noted in 4. There was no evidence of amyloid deposition, eosinophil infiltration, or other systemic inflammation.

3.5. Risk factors

There were 17 deaths (32.1%) and 5 cases of heart transplantation (9.4%) during the median follow-up of 1.7 years (interquartile range: 0.4–5.3). The overall 5-year survival rate was 64.4% ± 7.8%.

Although a previous study has shown that sex, NYHA Fc, LA diameter, and pulmonary congestion affect survival,[4] univariate analysis of sex, age, NYHA Fc, LA diameter and LV EF did not show a statistical significance in this study. However, pulmonary

Table 2

Univariate analysis of factors associated with death.

Variable	HR	95% CI	P
Sex	1.81	0.69–4.76	.231
Age	1.00	0.97–1.02	.835
NYHA Fc ≥ III	2.55	0.94–6.93	.066
Pulmonary congestion	3.24	1.13–9.33	.029
LVEF	0.98	0.95–1.02	.343
LVEDD	0.89	0.83–0.94	<.001
LA diameter	0.96	0.91–1.02	.164
TR ≥ moderate	7.08	2.25–22.32	.001
E/A	0.95	0.80–1.13	.559
DT	1.00	0.99–1.01	.549

A, peak velocity of the late filling wave due to atrial contraction; E, peak mitral flow velocity of the early rapid filling wave. CI = confidence interval, DT = deceleration time, HR = hazard ratio, LA = left atrial, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, NYHA Fc = New York Heart Association functional class, TR = tricuspid regurgitation.

Table 3

Multivariate analysis of factors associated with death.

Variable	HR	95% CI	P
NYHA Fc ≥ III	2.06	0.65–6.58	.220
Pulmonary congestion	2.42	0.77–7.58	.131
LVEDD	0.85	0.79–0.91	<.001
LA diameter	0.99	0.92–1.08	.864
TR ≥ moderate	32.55	6.69–158.69	<.001

CI = confidence interval, HR = hazard ratio, LA = left atrial, LVEDD = left ventricular end-diastolic diameter, NYHA Fc = New York Heart Association functional class, TR = tricuspid regurgitation.

congestion, LVEDD, and the presence of moderate or more TR were associated with mortality (Table 2). On multivariate analysis, pulmonary congestion, NYHA Fc, and LA diameter were found not to be associated with outcome. However, the risk of death was independently associated with moderate or more TR (hazard ratio [HR] 32.55, confidence interval [CI] 6.69–158.27, $P < .001$) and LVEDD (HR 0.85, CI 0.78–0.91, $P < .001$) (Table 3). Receiver-operating characteristic curves were used for setting the cutoff value for survival rate according to LVEDD. From receiver-operating characteristic analysis, the area under the curve was 0.74 ± 0.18 ($P = .006$, 95% CI 0.59–0.89); at LVEDD 46.5 mm, the sensitivity was 0.765 and specificity was 0.657, and this value was set as the cutoff.

The Kaplan–Meier survival curves showed the cumulative mortality among patients with moderate or more TR ($P = .001$) compared with those with less than moderate TR, and in patients with LVEDD <46.5 mm ($P = .019$) compared with those with LVEDD ≥46.5 mm (Fig. 1A, B).

4. Discussion

Idiopathic RCMP is a rare disease.[4,9] However, idiopathic RCMP has a large clinical implication because the prognosis was not as favorable as generally believed. Our study demonstrated a 5-year survival rate of 64.6% compared with the rate of 64% reported by Ammash et al.[4] Considering the time gap between our study and Ammash et al, there is no improvement in survival rate. Furthermore, no single drug has been found to improve the prognosis of idiopathic RCMP. Thus, a large-volume study about the prognosis needs to be conducted.

Idiopathic RCMP can be diagnosed when other etiologies for RCMP are ruled out. This causes the possibility of misdiagnosing other heterogeneous diseases as idiopathic RCMP. In our study, endomyocardial biopsy showed interstitial fibrosis and myocyte hypertrophy as the most common findings. However, these findings can also be found in hypertrophic cardiomyopathy or dilated cardiomyopathy. Genetic tests have the same problems. The genetic mutation observed in RCMP can be present in other cardiomyopathies.[10] Thus, idiopathic RCMP should be defined not only as a single finding of histology or genetic mutation but also according to functional impairment of the restrictive physiology of the ventricle with comprehensive clinical findings.

Some prognostic factors of idiopathic RCMP were reported before. In the study by Ammash et al,[4] the survival rates were lower in male patients and those with high-graded NYHA Fc, pulmonary congestion, and dilated LA dimension.[4] Moreover, the prognosis of idiopathic RCMP in children was poor with severe pulmonary hypertension.[11] However, in our study, the presence of TR and LVEDD affected prognosis. The group with moderate or more TR showed poor prognosis (HR 7.08, $P = .001$). In advanced TR, the preload of the right atrium increases, and sequentially the right atrium develops continuous volume overload. The RV filling pressure is already increased because of the restrictive physiology of RCMP. Consequently, TR further increases right ventricle end-diastolic pressure (RVEDP). These physiologic changes accelerate right atrial geometry change, which aggravates heart failure symptoms and probably affects survival. The most obvious need is to measure RVEDP through cardiac catheterization; however, only 5 patients underwent this test. The mean RVEDP was 10.40 mm Hg (normal range, 1–7 mm Hg).

Furthermore, we presented that small LV dimension (LVEDD <46.5 mm) was associated with poor prognosis. In normal or small LV, owing to increased passive stiffness of the LV, significant changes in pressure may be seen even with little or no detectable change in ventricular volume.[12] As Sherazi et al[13] reported, a smaller cavity in heart failure with preserved LV EF increased passive chamber stiffness. The small LV cannot accept venous return adequately, and such high LV filling pressure may worsen the symptoms of heart failure and lead to poor prognosis.
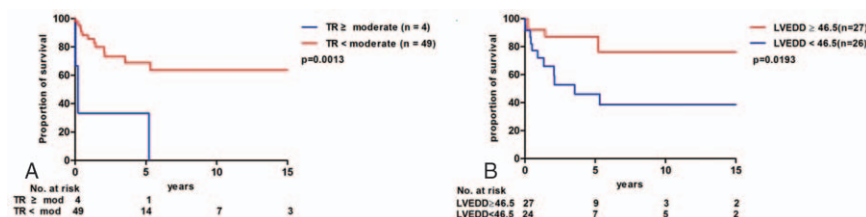

Figure 1. Cumulative survival rate according to TR and LVEDD in patients with idiopathic restrictive cardiomyopathy. LVEDD = left ventricular end-diastolic diameter, TR = tricuspid regurgitation.

5. Limitations

We considered that advanced TR and lower LVEDD are independent predictors of mortality in patients with idiopathic RCMP because these factors worsen the RV and LV filling pressures. However, the correlation between elevated ventricular filling pressure and mortality could not be confirmed, because cardiac catheterization was done in only 5 of 53 patients. In future studies, we suggest performing cardiac catheterization more aggressively.

As mentioned above, the RCMP diagnosis was established based on echocardiographic findings without any evidence of other RCMP. Invasive diagnostic methods may not be fully used depending on the clinical condition of the patient, consent for the test, and diagnostic strategy of each center. Therefore, bias due to the inclusion of cardiomyopathy of some other category that has a longer-term prognosis than RCMP may exist.

In addition, technical differences among echocardiographic devices may affect the evaluation of RCMP due to the prolonged period of analysis (1990–2010). Especially, tissue Doppler imaging contributes to more precise and earlier detection of the diastolic dysfunction which is important to evaluate restrictive physiology.[14,15] However, the measurement using tissue Doppler imaging was not sufficient in the early period of study. Therefore, there is the possibility that idiopathic RCMP was underdiagnosed.

6. Conclusions

The clinical characteristics of idiopathic RCMP in our multicenter study did not show significant differences compared with other previous studies. And the prognosis of idiopathic RCMP was still poor. Survival was found to be significantly adversely related to advanced TR and low LVEDD. The diagnosis of idiopathic RCMP was difficult and based on functional and morphological characteristics in our study. However, in future studies, a comprehensive approach including cardiac catheterization, biopsy, and gene mutation analysis is needed to rule out

other etiologies of RCMP, and obtain more accurate results on disease profile and prognostic factors.

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