Original Article

Epidemiology of Cardiomyopathy – A Clinical and Genetic Study of Restrictive Cardiomyopathy: The EPOCH-R Study

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Abstract

Introduction: Restrictive cardiomyopathy (RCM) is characterized by diastolic dysfunction, biatrial enlargement, and normal or near-normal systolic function. RCM is the rarest kind among cardiomyopathies with a severe outcome. **Methods:** Here, we present the clinical outcomes of thirty RCM patients recruited from a tertiary care unit of India, All India Institute of Medical Sciences, New Delhi. For clinical assessment, patients underwent electrocardiogram, echocardiography, and cardiac catheterization, and endomyocardial biopsy whenever required. **Results:** Out of 190 patients with cardiomyopathy, 100 had dilated cardiomyopathy, 60 had hypertrophic cardiomyopathy, and 30 had idiopathic RCM and were recruited for the study. Out of these thirty patients, 63.3% were males. A maximum number of patients were diagnosed in their second to third decade of life. Atrial fibrillation (73.3%) and ST-T abnormalities (76.6%) were common. Most of the patients showed the early age of onset with symptoms emerging in the first and second decades of life. Shortness of breath and fatigue were found to be common symptoms. No familial cases were found. **Conclusion:** RCM in India is a sporadic disease, rare, and occurs in the young. Prognosis of RCM is still worse than any other cardiomyopathy.

Keywords: Clinical phenotype, restrictive cardiomyopathy, sporadic

Introduction

Restrictive cardiomyopathy (RCM) is a rare phenotype among the cardiomyopathies. It is characterized as a disorder of myocardial muscles with impaired ventricular filling with distinct impaired hemodynamic features, raised filling pressures, and impaired diastolic dysfunction.[1-4] The classification of RCM is dependent on hemodynamic patterns which represents a challenge as other anatomical features may have a restrictive function as a common base.[5] A wide range of symptoms varying from patient to patient such as diminished exercise tolerance, dyspnea, edema, and palpitation has been reported.[2] Patients with idiopathic form usually lie in advanced heart failure stage, i.e., Class III and Class IV of the New York Heart Association (NYHA).[6] Nondistinctive histology can show normal findings or nonspecific degenerative changes including myocyte hypertrophy, disarray, and interstitial fibrosis.[7] In pediatric cases, RCM is the rarest phenotype with poor prognosis, accounts for 4.5% of the total cardiomyopathy cases. It has an excessively high morbidity and mortality.[8]

In countries like India, Africa, South, and Central America, the main cause of RCM is endomyocardial fibrosis rather than idiopathic form of RCM though the pattern is now changing.[7] Studies in the last decade have revealed that sarcomeric gene mutations are linked to cases of idiopathic RCM.[9-12] RCM in adults has a prolonged course of disease as compared to pediatric cases which often have shown poor prognosis with high mortality rate.[13,14] Females show a higher prevalence of idiopathic RCM than men (female:male ratio, 15:1). Due to the poor prognosis of pediatric cases' mean survival rate has been reported to range from months to 7.8 years.[13,15-18] Due to poor prognosis and variable response to pharmacological therapy, cardiac transplant remains the final treatment option.[19]

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Nearly 33%–60% of idiopathic RCM cases were reported to be caused by mutations in sarcomeric genes, with many overlapping genes and variants shared between RCM and hypertrophic cardiomyopathy (HCM). Many earlier studies reported the mixed phenotype of RCM and HCM even in the same families.[10] To study RCM as a rare entity always has its limitation with small sample sizes. Here, we represent the first clinical genetic report of a cohort of 30 RCM cases from India.

Methods

From our cohort of cardiomyopathy patients, we present RCM patients as an epidemiology of cardiomyopathy study-RCM (EPOCH-R) in the third phase after dilated[20] and HCM.[21] All participants were consecutive patients Figure 1 who underwent initial diagnostic workup, recruited from year 2012 to 2015 December. Diagnostics evaluation includes 12-lead electrocardiogram (ECG), two-dimensional echocardiography, and chest X-ray with histopathology test whenever required for diagnosis. During recruitment, family history was obtained with symptoms related to disease such as dyspnea, chest pain, palpitations, presyncope, and syncope. Patients were followed for 3 years. The study protocol was approved by Ethics Review Boards of both participating institutions of the study, and written consent forms were obtained, after explaining study details, from all the participating patients and their first-degree relatives.

The diagnosis of idiopathic RCM was based on fulfilling the below-given criteria: (1) biatrial enlargement, (2) markedly elevated ventricular filling pressures with characteristic restrictive hemodynamic pattern, (3) dilated inferior vena cava, and (4) restrictive Doppler flows, with preserved systolic function. Patients with ischemic heart disease, hypertension treated for 5 years, organic valvular disease, congenital or pericardial disease with any secondary RCM causing disease such as amyloidosis, and eosinophilic syndrome were excluded from the study.

Data were collected with a prescribed format for all the patients participated in the study.

For genetic analysis, 5 ml of intravenous blood was collected from patients and available family members with written informed consent. Five milliliters blood was subjected to DNA extraction from phenol–chloroform method.[22] Primers were in-house designed and are available on request. MYH7 hotspot region of cardiomyopathies, i.e., exon 23 was sequenced with the help of Sanger sequencing method (ABI 373 XL) of thirty patients. Another 100 clinically unaffected controls and family members of the patients in which variants were found also sequenced.

Sanger sequencing method is the gold standard method of determining the order of nucleotide bases (adenine, guanine, cytosine, and thymine). The method involves the synthesis of complementary DNA strand using 3' deoxynucleotide and terminates due to dideoxynucleotides. The four of the dideoxynucleotides are labeled with fluorescent dyes, and all of them emit light at different wavelengths, thus causing base-specific signaling which can be automatically recorded by a detector.

Results

Demographic characterization of patients

Thirty patients from the cohort of cardiomyopathy patients met the criteria for idiopathic form of RCM and thus are included in the study. Table 1 represents the demographic characteristics of patients. Out of thirty patients, 63.3% represent males and 36.6% were females. The mean age among patients was 31 ± 14.67, and 21.7% cases had an early age of onset. Age of onset in male (29.85 ± 14.4) was lower than female (31.6 ± 14.4) patients. Few patients showed very early age onset, i.e., 21.7% were under 20 years while one patient was only 11 years old. Most of the patients were literate and 16.6% were illiterates. Maximum percentage of patients was from upper middle class with 46.6% than lower middle class (26.6%), upper lower (23.3%), and only one patient in lower class [Table 1].

Table 1: Demographic variables of restrictive cardiomyopathy patients

Variables	Cases, *n* (%)
Number of individuals	30 (100)
Present age (mean±SD)	31±14.67
Age of onset (mean±SD)	30.3±14.44
Male age at onset (mean±SD)	29.85±14.85
Female age at onset (mean±SD)	31.63±14.4
Age-wise distribution (age at onset)	
0-20	8 (26.73)
21-30	9 (30)
31-40	6 (20)
41-50	3 (10)
50 above	4 (13.3)
Sex	
Male	19 (63.3)
Female	11 (36.6)
Marital status	
Married	15 (50)
Unmarried	15 (50)
Education status	
Postgraduates or above	1 (3.33)
Graduates	9 (30)
Intermediate	4 (13.3)
High school	8 (26.6)
Middle class	3 (10)
Illiterate	5 (16.6)
Socioeconomic status	
Upper	0
Upper middle	14 (46.6)
Lower middle	8 (26.6)
Upper lower	7 (23.3)
Lower	1 (3.3)

SD: Standard deviation

Clinical characterization of restrictive cardiomyopathy patients

Most of the RCM patients Table 2 were in the NYHA Class II, i.e., 63.3% while 33.3% were Class III and only 3.33% were Class IV. Table 2 represents the clinical characters of RCM patients. RCM patients showed a wide range of clinical symptoms such as chest pain, shortness of breath, palpitation, fatigue, arrhythmias, presyncope, syncope, and edema. However, fatigue (66.4%), palpitation (53.3%), and shortness of breath (63.3%) were highest among the patients. Chest pain (40%), arrhythmia (40%), and edema (43.3%) were present in fewer patients, whereas presyncope (16.6%) and syncope (16.6%) symptoms were least present among patients.

ECG was performed in all thirty patients and their family members. The most common features present were atrial fibrillation (73.3%), ST-T changes (76.6%), and abnormal sinus rhythm (60.6%). Tachycardia (60.6%) was more common than brachycardia (13.3%). Both left axis deviation (43.3%) and right axis deviation (36.6%) were present. Left bundle branch block (60%) were present in much more patients than right bundle branch block (43.3%). However, in our cohort, atrioventricular block was present in very less percentage (33.3%) among patients, and abnormal Q waves were also seen only in a few patients (36.6%).

On echocardiography examination, the mean left ventricular end-diastole diameter (LVED) was 42.8 ± 8.43 and only increased aorta thickness was 24 ± 3.7. The mean posterior wall (PW) thickness (LVED) was 10.9 ± 2.2, and interventricular septum (IVS) thickness (11.1 ± 2.33) was normal or near normal. Mean ejection fraction among RCM patients was lower than normal, i.e., 50.8 ± 11.5. Both left (76.6%) and right (80%) atria were enlarged in most of the patients. Left ventricle (40%) and right ventricle (20%) were also seen to be enlarged in some patients. Mitral valve regurgitation was absent in 40% patients, mild in 30% patients, moderate in 10%, trivial in 16.6%, and severe in 23.3%. Tricuspid regurgitation was absent in 36.6%, mild in 30%, moderate in 6%, trivial in 3.3%, and severe in 23.3%. Aortic regurgitation was absent in 93.3% patients and present as trivial in only 6.6%.

In our study, ten patients were transformed in a severe form of disease and were listed for the heart transplant, and two died at an early age of 11 years and 9 years old due to sudden cardiac

Table 2: Clinical symptoms of restrictive cardiomyopathy cases

Variable	Cases, *n* (%)	ECG variables	Cases, *n* (%)
NYHA class		Atrial fibrillation	22 (73.33)
Class I + II	19 (63.3)	ST-T changes	23 (76.6)
Class III + IV	11 (36.6)	Abnormal sinus rhythm	20 (60.6)
Symptoms		Tachycardia	20 (60.6)
Chest pain	12 (40)	Brachycardia	4 (13.3)
Shortness of breath	19 (63.3)	Left axis deviation	13 (43.3)
Palpitation	16 (53.3)	Right axis deviation	11 (36.6)
Fatigue	20 (66.6)	AV block	10 (33.3)
Arrhythmia	12 (40)	LBBB	18 (60)
Presyncope	5 (16.6)	RBBB	13 (43.3)
Syncope	5 (16.6)	Abnormal Q wave	11 (36.6)
Edema	13 (43.3)		
Echocardiography variables			
		RV chamber	
		Enlarged	6 (20)
IVS (10 mm)	11.1±2.33	Normal	24 (80)
Ejection fraction (62-80%)	50.8±11.5	Mitral valve regurgitation	
LAes (21-22 mm/m^2)	40.4±12	Absent	12 (40)
LVED (19-32 mm/m^2)	42.8±8.43	Mild	9 (30)
PW (LVED) (17-11 mm)	10.9±2.2	Moderate	3 (10)
LV chamber		Trivial	5 (16.6)
Hypertrophied	12 (40)	Severe	1 (3.3)
Normal	18 (60)	Tricuspid valve	
LA chamber		Absent	11 (36.6)
Enlarged	23 (76.6)	Mild	9 (30)
Normal	7 (23.3)	Moderate	2 (6)
RA chamber		Trivial	1 (3.3)
Enlarged	24 (80)	Severe	7 (23.3)
Normal	6 (20)		

NYHA: New York Heart Association, ECG: Electrocardiogram, LBBB: Left bundle branch block, RBBB: Right bundle branch block, RA: Right atrial, LV: Left ventricular, AV: Atrioventricular, PW: Posterior wall, LA: Left atrial, LVED: Left ventricular end-diastole diameter

Table 3: Previous genetic studies for restrictive cardiomyopathy

Study	Patients	Brief detail of the study
Mogensen *et al*., 2003[10]	9 RCM patients	This study identifies the restrictive cardiomyopathy as a part of spectrum of sarcomeric genes and found TNNI3 gene to be associated with restrictive physiology
Zhang *et al*., 2005[40]	13RCM patients	This study reports chromosome 10 as a genome-wide linkage association, but no genes were found in this interval to cause restrictive cardiomyopathy
Peddy *et al*., 2006[11]	1 RCM patient	In this study, eight sarcomeric genes were sequenced and found a novel in-frame 285-287 GGA deletion in exon 9 of TNNT2 gene
Cubero *et al*., 2007[41]	1 RCM patient	This study reports case of a 54-year-old male diagnosed with restrictive cardiomyopathy without skeletal myopathy. On genetic analysis of TNNI3 coding, sequence revealed no mutations
Kubo *et al*., 2007[9]	16 RCM patients	This study analyzed five sarcomeric genes in 16 RCM patients and found four mutations in TNNI3 gene and four in MYH7 gene
Kaski *et al*., 2008[42]	12 RCM patients	This study screened for mutation in eight sarcomeric genes and found two mutations in TNNI3, one in ACTC, and one in TNNT2 gene
Karam *et al*., 2008[43]	1 RCM patient	This study reports first pediatric case associated with a *de novo* mutation p.P838L in MYH7 gene
Ware *et al*., 2008[44]	1 RCM patient	This study reported sequencing of eight sarcomeric genes and found heterozygous mutation G768R associated with severe form of disease
Menon *et al*., 2008[45]	1RCM family	This study represents the unique family with heterozygous missense mutation I79N in TNNI3 gene in a family with a variable expression in the family with five different cardiomyopathy phenotype
Kostareva *et al*., 2009[46]	1 RCM patient	This study used candidate gene approach and found a novel one nucleotide deletion nt4762delG resulting in frameshift causing deletion of a part of exon 7 and 8 of TNNI3 gene
Rai *et al*., 2009[47]	10 RCM Patients	This study represents the RCM patients analyzed for genetic mutation in selected exons of TNNI3, and MYH7 gene revealed one mutation p.Arg721Lys to be associated with severe form of disease with sudden cardiac death
Yang *et al*., 2010[48]	1 RCM patient	This study reports the infantile case of ventricular septal defect and restrictive cardiomyopathy to be associated with *de novo* mutation p.R204H in TNNI3 gene
Caleshu *et al*., 2011[37]	2 RCM patients	This study represents the association of the TPM1, MYL2, and MYL3 genes with nonhypertrophied restrictive cardiomyopathy
Van den Wijngaard *et al*., 2011[49]	4 RCM cases	This study sequenced TNNI3 gene in cardiomyopathy patients including 4 RCM patients found frequency of 3%
Peled *et al*., 2014[50]	1 RCM family	In this study, after segregation of locus in affected individuals showed common segregation around TTN gene. Sequence analysis of TTN gene revealed p.Y7621C variant in exon 266. This was the first report of association of RCM phenotype with TTN gene mutation
Wu *et al*., 2015[51]	2 RCM patients	This study reports MYBPC3 gene mutations in a family with three live patients and one unrelated patient
Brodehl *et al*., 2016[52]	2 RCM patients	In this study, with the help of NGS, two novel mutations in FLC gene in two families of autosomal-dominant RCM
Mouton *et al*., 2015[53]	100 RCM patients	This study identified a novel p.Leu144His mutation and a *de novo* p.Arg170Gln mutation associated with RCM and focal ventricular hypertrophy in South African population
Yu *et al*., 2016[54]	15 RCM patients	This study identifies the TMEM43 gene to be associated with a rare form of autosomal-recessive form of RCM
Ruan *et al*., 2016[55]	1 RCM family	This study identified mutation p.S150P in a Chinese family with 5 RCM patients in exon 7 of gene TNNI3. This mutation was not found in 200 control subjects and segregated in the family with the disease
Kostareva *et al*., 2016[56]	24 RCM patients	This study investigated 108 cardiomyopathy-associated genes in 24 RCM patients with the help of NGS and found 54% of positive genotype correlation
Ploski *et al*., 2016[57]	1 RCM patient	This study represents the pediatric case of HCM which eventually progressed into severe form of RCM associated with p.D145E in TNNC1 gene
Ouellette *et al*., 2018[58]	8 RCM patients	Compared expanded panel testing and targeted panel testing and found not much differences in the results. However, 25% of RCM cases found pathogenic variants
JurcuŢ *et al*., 2017[59]	1 RCM patients	A novel heterozygous variant c. 1297C > A, p.(Pro433Thr) was found to be associated with severe form RCM and skeletal myopathy
Hwang *et al*., 2017[60]	1 RCM family	This study represents the TNNI3 gene mutation c. 433C > T with elder sister died due to RCM. On family screening, six other family members found to be carriers of the TNNI3 mutation
Brodehl *et al*., 2017[61]	1 RCM family	This study identifies the novel association of CRYAB mutation p.D109G with RCM in a small family using NGS
Kapoor *et al*., 2017[23]	2 RCM patients	This study identifies the one rare and novel compound heterozygous variant in two unrelated RCM sporadic cases in exon 23 of MYH7 gene

RCM: Restrictive cardiomyopathy, HCM: Hypertrophic cardiomyopathy, NGS: Next-generation sequencing, FLC: Fibrolamellar carcinoma

death. Clinical evaluation of patients and family members revealed 100% sporadic cases.

Sanger sequencing of the hotspot region of MYH7 gene

For genetic analysis, sequencing of hot spot region of MYH7 gene, i.e., exon 23 was done on 30 RCM patients and 100 controls. Mutations were found in two patients. No cases of familial RCM were found.

Sequencing of hotspot region exon 23 of MYH7 gene revealed one rare E949K variant in one patient. This rare variant E949K was found in an 11-year-old boy who had a sporadic case of RCM with an early age of onset and severe form of disease with sudden cardiac death. This variant was earlier reported to be associated with HCM with late onset of disease.[24] On clinical screening, parents were found to be unaffected, and the mutation was absent making it a *de novo* variant and a sporadic case.

In another patient, a compound heterozygous variant E902k and D906N novel variant was found in a 24-year-old lady with an early age of onset and disease who progressed from Class NYHA II to NYHA IV and was registered for heart transplant. Family screening revealed all members unaffected, and the variant was also absent in the family members. These variants were found in highly conserved region of MYH7 gene. *In silico* assessment of rare and compound heterozygous mutations found to be deleterious.

Discussion

Many classifications have come into light in the past few decades defining and classifying these cardiomyopathies according to the morphology and pathology. However, the European Heart Association defined five major types of cardiomyopathies in the classification such as HCM, dilated cardiomyopathy (DCM), RCM, arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathies Table 3.[25]

RCM has a variable age of onset and may develop at any age. Symptoms' severity may range from asymptomatic to severe symptoms. Major complaints of patients are shortness of breath, chest pain, and fatigue, with later development of pulmonary congestion, ascites, and decreased cardiac output. The diagnosis of this condition is rare in early stages[16] and usually made at later stages of the disease only making it more severe to handle with medications,[26] and in later stages, the treatment of choice left is heart transplantation.[27] Due to its scarcity and severe form, the opportunities to define its characters and pathology make it a difficult task. Idiopathic RCM has been reported with very small number of cases.[2,3,28,29]

Here, we report thirty cases of idiopathic RCM patients from a tertiary care unit of India, All India Institute of Medical Sciences, New Delhi. Idiopathic RCM was known to be more prevalent in females than males (1.5:1);[29] however, in our study, male preponderance is more with 2:1 ratio. Earlier studies reported familial occurrence in RCM as seen in HCM and DCM.[7] However, no familial case was reported in our study. Patient underwent series of clinical examinations such as ECG, echocardiography, and chest radiography, with endomyocardial biopsy whenever required. ECG abnormalities in RCM patients are usual. ST-T segment abnormalities are characteristic for RCM which reflect the abnormal diastolic function and repolarization abnormalities of the ventricular muscles.[7] Atrial fibrillation (73.3%) and ST-T abnormalities (76.6%) were the most common features present in this cohort. Abnormal sinus rhythm, left bundle branch block, and left axis deviation were present in 40%–50% patients. In the chest X-ray, appearance of mild-to-moderate cardiomegaly was the common feature seen in patients due to the presence of atrial enlargement. Echocardiography is a noninvasive method of choice for the diagnosis of cardiomyopathies. The diagnosis is based on the characteristics such as nondilated, nonhypertrophied with biatrial enlargement. Consistent with earlier reports, marked atrial enlargement was present in 76.8% of patients in our cohort and found to be prominent finding.[3,30-32] With or without diastolic equalization, elevated diastolic pressures are a common feature present in symptomatic patients[3,33,34] as seen in our cohort with elevated diastolic pressures are a prominent diagnostic feature. The normal or near normal PW (LVED) and IVS thicknesses provide the basis of pure RCM without hypertrophy of heart.

RCM, as reported in earlier reports, seems to be a progressive disease over time.[3,34] As recommended, heart transplantation remains the method of choice in the absence of effective treatment.[15,29,35] Sudden cardiac death has been seen in patients with stable conditions.[13,15,29,35]

Latest development and advancement of molecular technologies, combining with genetic studies of cardiomyopathies in the past three decades, has revealed a genetic basis as the direct cause of many idiopathic cardiomyopathies.[36] In the past decade, all eight sarcomere genes have been associated with the cause of RCM.[37] In a recent report, we sequenced the hotspot region of MYH7 gene, i.e., exon 23 and one rare (E949K) and two novel compound heterozygous (E902K and D906N) variants were identified.[23] E949K variant was earlier reported to be associated with HCM patient with late age of onset;[24] however, we found this to be associated with a RCM phenotype without hypertrophy and early age of onset of disease.[23] In recent reports, many studies have shown the compound heterozygous and double heterozygous mutations to be associated with RCM.[38,39] Compound heterozygote mutations were known to cause early age of onset and severe form of disease in cardiomyopathies as seen in our patient present with early age of onset and severe symptoms.[40]

However, more extensive genetic studies with a holistic approach need to be done to understand the pathophysiological mechanism of cardiomyopathies. Next-generation sequencing provides the technique to study the whole genome and exome to understand more fully the genetic basis of cardiomyopathies.

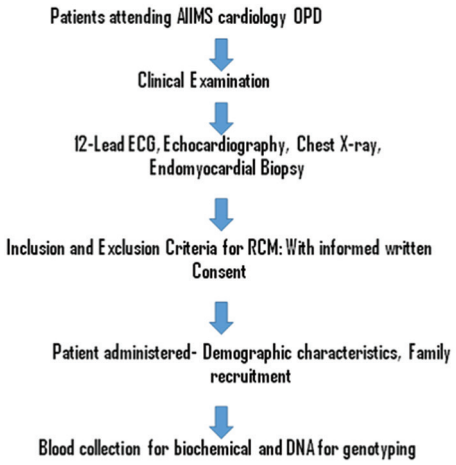

Figure 1: Flowchart to identify restrictive cardiomyopathy patients through proper clinical procedures and methods on the basis of inclusion/exclusion criteria of restrictive cardiomyopathy and collection of blood samples.

Conclusion

RCM emerged as a genetic disorder in the past decade. Prognosis of RCM is still worse than any other cardiomyopathy with male preponderance. No familial cases were found and 100% are sporadic. Most of the patients showed the early age of onset as symptoms emerged in the first and second decade of life. Shortness of breath and fatigue found to be common symptoms. Genetic screening of the MYH7 exon 23 hotspot regions could only explain 6.6% of RCM cases. To understand the pathophysiological mechanism of cardiomyopathies, the combinations of thorough clinical and genetic studies are the need of the hour.

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Conflicts of interest

There are no conflicts of interest.

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