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ORIGINAL ARTICLE

Hypokinetic hypertrophic cardiomyopathy: clinical phenotype, genetics, and prognosis

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Abstract

Aims To describe the phenotype, genetics, and events associated with the development of hypertrophic cardiomyopathy (HCM) with reduced ventricular function (HCMr). Heart failure in HCM is usually associated with preserved ejection fraction, yet some HCM patients develop impaired systolic function that is associated with worse outcomes.

Methods and results Our registry included 1328 HCM patients from two centres in Spain and Israel. Patients with normal baseline ventricular function were matched, and a competing-risk analysis was performed to find factors associated with HCMr development. Patient records were reviewed to recognize clinically significant events that occurred closely before the development of HCMr. Genetic data were collected in patients with HCMr. A composite of all-cause mortality or ventricular assist device (VAD)/heart transplantation was assessed according to ventricular function. Median age was 56, and 34% were female patients. HCMr at evaluation was seen in 37 (2.8%) patients, and 46 (3.5%) developed HCMr during median follow up of 9 years. HCMr was associated with younger age of diagnosis, poor functional class, and ventricular arrhythmia. Atrial fibrillation, pacemaker implantation, and baseline left ventricular ejection fraction (LVEF) of ≤55% were significant predictors of future HCMr development, while LV obstruction predicted a lower risk. Genetic testing performed in 53 HCMr patients, identifying one or more pathogenic variant in 38 (72%): most commonly in myosin binding protein C (n = 20). Six of these patients had an additional pathogenic variant in one of the sarcomere genes. Patients with baseline HCMr had a higher risk (hazard ratio 6.4, 4.1–10.1) for the composite outcome and for the individual components. Patients who developed HCMr in the course of the study had similar mortality but a higher rate of VAD/heart transplantation compared with HCM with normal LVEF.

Conclusions Hypertrophic cardiomyopathy with reduced ejection fraction is associated with heart failure and poor outcome. Arrhythmia, cardiac surgery, and device implantation were commonly documented prior to HCMr development, suggesting they may be either a trigger or the result of adverse remodelling. Future studies should focus on prediction and prevention of HCMr.

Keywords Hypertrophic cardiomyopathy; Heart failure; Systolic dysfunction; Genetics

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Tweet: *HCM with reduced ejection fraction is associated with poor functional and exercise capacity, and poor outcome. Arrhythmia, cardiac surgery and device implantation may be either a result or a trigger of adverse remodeling. #HCM #HeartFailure #CardioTwitter*

Introduction

Hypertrophic cardiomyopathy (HCM) is a structural heart disease defined by an increase in left ventricular (LV) wall thickness in the absence of other causes of secondary hypertrophy such as hypertension. The estimated prevalence of HCM is roughly 1:500, and a pathogenic variant in sarcomere protein genes may be identifiable in up to 60% of cases.[1–3] In a minority of cases, an HCM-like phenotype may be associated with a myriad of genetic and non-genetic aetiologies,

including infiltrative heart disease such as amyloidosis, metabolic disorders, and congenital syndromes.

Hypertrophic cardiomyopathy may evolve or clinically present at almost any age. Classically, HCM is associated with a small LV cavity, hyperdynamic contraction, and LV outflow tract obstruction at rest or with provocation.[4] The disease course may be complicated by functional limitation, heart failure, and arrhythmia, which may result in stroke or sudden cardiac death.[4] Using contemporary management strategies, HCM is generally considered to have low rates of disease related mortality.[5] Yet some patients progress to advanced disease characterized by reduced LV systolic function (HCMr), with or without ventricular dilatation. This condition is often referred to as *end-stage* HCM, *hypokinetic* HCM, or 'burned-out cardiomyopathy' and is invariably associated with higher rates of morbidity and mortality.[6] Nevertheless, contemporary data suggest that novel interventions may improve the outcomes in this population.[7,8]

The factors responsible for developing end-stage HCM are not well known. It was reported to be associated with early disease onset, greater wall thickness, and family history of HCM.[9] Olivotto *et al*.[10] showed that myocardial ischaemia on perfusion imaging is associated with subsequent loss of LV function. Genetic factors such as certain *malignant* mutations[11] and multiple pathogenic variants are another cause of disease progression and adverse outcomes. There are currently over 1500 genetic variants associated with HCM, mainly in genes encoding sarcomere proteins. Sarcomere protein gene mutations are associated with a younger age of disease onset, greater LV hypertrophy, a more familial disease pattern, and more sudden cardiac death.[12] The combination of early age of disease onset and a recognized sarcomere mutation has been associated with poor outcomes in the large contemporary Sarcomeric Human Cardiomyopathy Registry (SHaRe).[13]

We hereby report on the prevalence, clinical predictors, and possible precipitating factors, of developing an HCMr in a large binational cohort of patients with a long-term follow up.

Methods

Study population

Consecutive HCM patients were enrolled into a computerized registry of two tertiary medical centres: The Chaim Sheba Medical Center in Tel-HaShomer, Israel (during 2004–2020), and The Complexo Hospitalario Universitario A Coruña, Spain (2000–2020). Initially, we registered the patients who were already followed in the Cardiomyopathy/Heart Failure clinic. All new patients were prospectively included. As previously described, there were no significant differences between the HCM cohorts from the two countries.[14]

Clinical, electrocardiographic (ECG) and echocardiographic data were acquired upon admission for evaluation in the cardiomyopathy clinic. Follow-up data on heart transplantation, resuscitated sudden death, and device implantation were collected from Hospital, Cardiomyopathy, Heart Failure or Electrophysiology Clinics patient records. Mortality data were obtained from the National Registries.[14]

The diagnosis of HCM required an unexplained LV wall thickness of $\geq$15 mm or $\geq$13 mm in the presence of a first degree family member affected by HCM.[4] Obstructive cardiomyopathy was defined as resting LV outflow gradient $\geq$ 30 mmHg.

Patient evaluation, treatment, device implantation, and interventions were conducted according to consensus clinical indications and contemporary HCM guidelines.[4] Gene testing was performed within the framework of clinical management considering the patient's preference, institutional policy, financial coverage, and the presence of a known pathogenic variant in family members with HCM.

Hypokinetic HCM (HCMr) was defined by LV ejection fraction (LVEF) $<$ 50% in two or more consequent echo-Doppler studies in the absence of acute injury such as acute myocardial infarction and sustained tachyarrhythmia. The study group was composed of patients who had HCMr at baseline evaluation (HCMrb) in the cardiomyopathy clinic, and those who presented with a LVEF within normal range, and developed HCMr during follow up (HCMrf). Patients diagnosed with infiltrative disease (i.e. cardiac amyloidosis) or suffering from hypertension or valvular disease, considered to account for or significantly contribute to left ventricle hypertrophy, were excluded.

Goals

The primary goal of our study is to describe the clinical phenotype and medical events associated with the development of HCMr in comparison with HCM population with remained with normal systolic function through the follow-up period (HCMn). Our secondary goals were to examine the relation between pathogenic genetic variants and HCMr and the correlation between HCMr and long-term HCM-related outcomes and mortality.

Ethics

The study was approved by the local institutional ethics committees. Patients were managed according to contemporary HCM guidelines and clinical practice guidelines published by national and international professional societies,

Statistical analysis

All variables were described according to their properties as previously described.[14] In order to control for the inherent differences and to account for multiple confounders between HCM patients normal range baseline EF who either developed or did not develop HCMr during follow up, we established a propensity score for age over 60 years, gender, obesity (defined as body mass index $>$ 30), a personal history of ischaemic heart disease, diabetes mellitus, and chronic kidney disease. Matching was performed using the nearest neighbour method, assigning patients with diabetes and without diabetes in a 1:5 ratio, with a 0.1 calliper width.

Survival analysis was performed by one of several methods. For the primary composite outcome of all-cause mortality, heart transplant or implantation of a ventricular assist device, and for the component of all-cause mortality, we performed a Cox-regression model. For the component of either heart transplant or implantation of a ventricular assist device, we performed a competing-risk assessment based on the model by Fine and Gray.[15] described graphically by using the Kaplan–Meier survival analysis method with a *P* log-rank test when adequate.

Because of large variability in the time and extent of genetic testing (familial variant, candidate gene(s), sarcomere screen, cardiomyopathy panel, etc.), data analysis was restricted to *pathogenic* or *likely pathogenic* variants in sarcomere protein genes and other established causes of LV hypertrophy, classified according to consensus recommendations.[16]

The statistical analysis was carried out with the use of R Version 4.0.3 software (The R Foundation) and R-studio 1.3.1093 (RStudio, Inc).

Results

Our initial analysis included 1328 patients (771 from Spain and 617 from Israel), with a median age of 56 years [interquartile range (IQR) 43–66], 458 patients (34%) female. Median follow up was 9 years (5.3–12.4). Thirty-seven patients (2.8%) had HCMr at their baseline evaluation in the cardiomyopathy clinic (hence HCMrb). In 30 of them, there was a documentation of normal LVEF at the time of initial diagnosis of HCM, while 7 had impaired LV function during their HCM diagnosis. Another 46 (3.5% of the entire HCM cohort) developed HCMr during follow up (hence HCMrf). In this subgroup, the first documentation of reduced LVEF took place 8.6 ± 5.8 years from initial evaluation. *Figure 1* illustrates the age-dependent incidence of HCM and the projected age-dependent prevalence of hypokinetic HCM in our cohort.

Clinical characteristics

Patients with HCMr at their initial evaluation in cardiomyopathy clinic were younger at the time of HCM diagnosis, predominantly male, had a lower body mass index, as well as higher prevalence of familial history of both HCM and sudden cardiac death. They had more prior sustained ventricular tachyarrhythmia as well as pacemaker and defibrillator implantations. Patients who had normal LV function at their first evaluation, and later developed HCMr during follow up had more history of atrial fibrillation, non-sustained ventricular tachycardia and implanted pacemakers and defibrillators when compared with those who maintained normal LVEF (HCMn) during follow up (*Table 1*).

On ECG, patients with HCMn had more frequent sinus rhythm, shorter PR interval, and QRS durations and had less intraventricular conduction defects, compared with both HCMr groups. Importantly, these parameters significantly differed at baseline evaluation between HCMn and HCMrf patients at the time when both groups had an LVEF in the normal range (*Table 2*).

There were pronounced differences in echocardiographic parameters. The LV wall thickness was lower in patients with HCMrb compared with those with normal baseline LVEF. While HCMrf had their initial LVEF in the normal range [58% (IQR 50–62%)], it was significantly lower than in HCMn [median 65%, (IQR 60–73%)]. Both HCMr groups had a lower prevalence of LV outflow obstruction. Concomitantly, there was an increase in the LV dimensions, left atrial enlargement, as well as pulmonary hypertension (*Table 2*). Noteworthy, there were no apparent differences in estimated diastolic dysfunction or the degree of mitral regurgitation.

Finally, patients with HCMr at their baseline evaluation had a significantly worse NYHA functional class, a lower exercise capacity, and often had an abnormal blood pressure response to exercise. The two groups presenting with normal LVEF did not differ in these parameters (*Table 2*).

At baseline, there were no significant differences in medical management between patients with normal LVEF and those with HCMrb. Patients who developed HCMr at follow up had higher rates of anticoagulation therapy and angiotensin-converting enzyme inhibitor therapy compared with patients in the HCMn group. Rates of previous catheter ablation therapy for either atrial fibrillation or atrial flutter were higher in both HCMr groups compared with HCMn obviously reflecting the prevalence of atrial tachyarrhythmia (Supporting Information, *Table S1*).

Predictors of hypertrophic cardiomyopathy with reduced ventricular function

In order to identify predictors for the development of HCMr while minimizing the impact of potential clinical covariables,

Figure 1 Age of diagnosis and projected prevalence of reduced left ventricular ejection fraction. HCMr, hypertrophic cardiomyopathy with reduced ejection fraction; (*A*) Age of the diagnosis of hypertrophic cardiomyopathy; (*B*) Projected incidence of reduced left ventricular ejection fraction based on the prevalence of hypokinetic HCM by age.

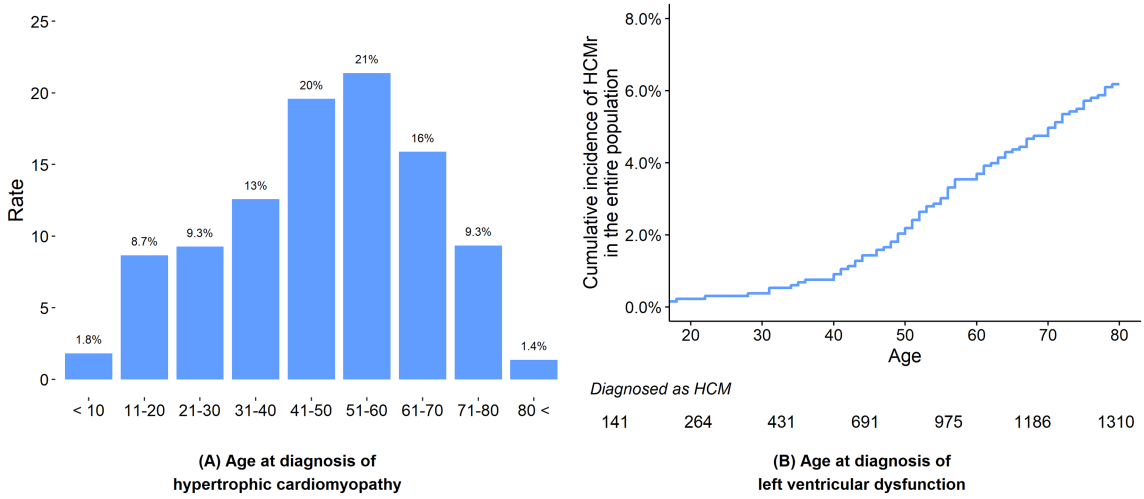


Table 1 Baseline characteristics

	HCMn (n = 1245)	HCMr during follow up (n = 46)	P^a	HCMr at baseline (n = 37)	P^b
Age of diagnosis	49 (35–60)	46 (26–60)	0.285	30 (17–44)	<0.001
Age of evaluation	56 (43–67)	55 (45–66)	0.590	53 (44–58)	0.403
Female gender	435 (35%)	17 (37%)	0.901	6 (16%)	0.028
Body mass index	28 (25.1–31.1)	27.7 (25.1–30.5)	0.520	24.7 (23.4–27.5)	<0.001
Diabetes mellitus	106 (9%)	3 (7%)	0.836	3 (8%)	1.000
Hypertension	463 (37%)	15 (33%)	0.625	6 (16%)	0.015
Hyperlipidaemia	442 (36%)	17 (37%)	1.000	10 (27%)	0.331
Current smoker	256 (22%)	7 (16%)	0.501	5 (14%)	0.328
Coronary artery disease	58 (5%)	2 (4%)	1.000	3 (8%)	0.559
Stroke	83 (7%)	7 (15%)	0.052	4 (11%)	0.567
COPD	39 (3%)	1 (2%)	1.000	0 (0%)	0.549
Chronic kidney disease	36 (3%)	0 (0%)	0.475	3 (8%)	0.163
Angina	412 (33%)	15 (33%)	1.000	7 (19%)	0.102
History of syncope	204 (16%)	11 (24%)	0.253	5 (14%)	0.778
Atrial fibrillation	321 (26%)	25 (54%)	<0.001	13 (35%)	0.348
Non-sustained VT	225 (18%)	18 (39%)	0.001	11 (30%)	0.147
Sustained VT VF	26 (2%)	2 (4%)	0.605	8 (22%)	<0.001
Family history of HCM	493 (40%)	24 (52%)	0.120	25 (68%)	0.001
Family history of SCD	221 (18%)	13 (28%)	0.113	12 (32%)	0.050
Permanent pacemaker	134 (11%)	15 (33%)	<0.001	15 (41%)	<0.001
Implanted defibrillator	152 (12%)	17 (37%)	<0.001	19 (51%)	<0.001

COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HCMn, HCM with normal ejection fraction; HCMr, HCM with reduced ejection fraction; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
Categorical variables are described as *n* (%). Continuous variables are described as median (IQR) or mean (±SD). Refer to *Methods* section for further clarifications.
[a]Comparing both groups with normal baseline ejection fraction.
[b]Comparing patients by left ventricular function at first evaluation.

we created a matched cohort to compare the two groups with normal baseline LVEF (*Table S2*, refer to *Methods*). After matching for age, gender, coronary artery disease, diabetes, renal failure, and obesity at baseline, the patients with HCMrf had more history of atrial fibrillation (53% vs. 27% in HCMn, P = 0.001), history of non-sustained VT (40% vs. 21%, P = 0.01), permanent pacemakers (33% vs. 8%, $P < 0.001$), and implanted defibrillator (36% vs. 12%, $P < 0.001$). The groups had no significant difference in functional and exercise capacities (*Table S2*). The comparison of ECG and

Table 2 Functional and exercise capacity, electrocardiography, and echocardiography

		HCMn (n = 1245)	HCMr during follow up (n = 46)	P^a	HCMr at baseline (n = 37)	P^b
Electrocardiogram	LV hypertrophy pattern	578 (55.8%)	15 (46.9%)	0.409	12 (37.5%)	0.065
	P-mitrale	246 (34.4%)	6 (33.3%)	1.000	15 (60.0%)	0.015
	Sinus rhythm (at admission)	976 (86.1%)	25 (56.8%)	<0.001	14 (56.0%)	<0.001
	PR interval (ms)	164 (148–182)	180 (160–190)	0.067	200 (144–250)	0.024
	QRS duration (ms)	98 (88–110)	120 (100–149)	0.001	106 (96–150)	0.005
	Atrioventricular block > 1st degree	34 (3.4%)	4 (12.5%)	0.026	3 (8.6%)	0.297
	Left anterior fascicular block	54 (5.4%)	4 (12.9%)	0.164	2 (5.7%)	1.000
	Right bundle branch block	105 (10.5%)	5 (16.1%)	0.478	2 (5.7%)	0.511
	Left bundle branch block	66 (6.6%)	9 (29.0%)	<0.001	5 (14.3%)	0.220
	Interventricular conduction delay	96 (9.6%)	8 (25.8%)	0.008	11 (31.4%)	<0.001
Echocardiograph	LV diastolic dimension (mm)	44 (40–49)	48 (43–53)	<0.001	54 (48–58)	<0.001
	LV systolic dimension (mm)	26 (22–30)	32 (28–35)	<0.001	39 (32–46)	<0.001
	Septal thickness (mm)	17 (14–20)	18 (15–21)	0.270	14 (12–17)	<0.001
	Posterior wall thickness (mm)	11 (10–13)	12 (10–13)	0.858	11 (10–13)	0.942
	Maximal LV wall thickness (mm)	18 (16–21)	20 (16–22)	0.226	16 (14–19)	0.009
	LV ejection fraction (%)	65 (60–73)	58 (50–62)	<0.001	35 (30–43)	<0.001
	Left atrial diameter > 40 mm	816 (69.9%)	38 (84.4%)	0.053	33 (94.3%)	0.004
	Obstructive HCM	491 (41.4%)	6 (13.3%)	<0.001	4 (10.8%)	0.001
	Apical HCM	86 (6.9%)	4 (8.7%)	0.863	0 (0.0%)	0.183
	Mitral insufficiency > mild	158 (23.8%)	3 (18.8%)	0.861	6 (18.8%)	0.665
	Diastolic dysfunction	539 (43.3%)	15 (32.6%)	0.198	18 (48.6%)	0.599
	Estimated SPAP > 40 mmHg	171 (13.7%)	10 (21.7%)	0.187	14 (37.8%)	<0.001
Functional and exercise capacity	NYHA class I	519 (42.0%)	22 (47.8%)	0.735	5 (13.5%)	<0.001
	II	502 (40.6%)	17 (37.0%)		11 (29.7%)	
	III[c]	214 (17.3%)	7 (15.2%)		21 (56.8%)	
	Exercise capacity (METs)	10 (7–12)	9 (6–10)	0.193	5 (4–10)	0.009
	Abnormal blood pressure response	253 (29.8%)	10 (32.3%)	0.922	10 (58.8%)	0.021

EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HCMn, HCM with normal ejection fraction; HCMr, HCM with reduced ejection fraction; LV, left ventricle.
Categorical variables are described as n (%). Continuous variables are described as median (IQR) or mean (±SD). Refer to *Methods* section for further clarifications.
[a]Comparing both groups with normal baseline ejection fraction.
[b]Comparing patients by left ventricular function at first evaluation.
[c]Including one patient with NYHA functional class IV.

echocardiographic features was similar to those seen in the unmatched population.

In a multivariate regression model in the matched population, a history of atrial fibrillation [hazard ratio (HR) 2.27, 95% confidence interval (CI) 1.2–4.2, P = 0.01], pacemaker implantation (HR 3.67, 95%CI 1.8–7.5, $P < 0.001$), and baseline LVEF of ≤55% (HR 4.58, 95%CI 2.4–8.8, $P < 0.001$) were significant predictors of future HCMr development, while having LV obstruction appeared to be protective (HR 0.24, 95%CI 0.1–0.6, P = 0.004; *Table 3*). Repeating the analysis considering the country of origin had no effect on the prediction model (*Table S3*).

Clinical events preceding the decrease in left ventricular ejection fraction

Cumulatively, patients with HCMr were diagnosed with HCM at a mean age of 38 (±19) years and were diagnosed with HCMr at a mean age of 56 (±15) years. Twenty-three (26%) of the 83 patients with HCMr were females. Female patients had less HCMr on baseline evaluation compared with male patients (*Table 1*), despite similar ages of initial HCM diagnosis. However, the age at first documentation of HCMr [male 56 years (48–67) vs. female 55 years (43–72), P = 0.78], as well as duration of known HCM before hypokinetic transformation did not differ significantly between the genders [male 18 years (7–26) vs. female 18 years (7–27), P = 0.91].

We examined the medical charts to identify the events that temporarily preceded and therefore could be related to the development of hypokinetic transformation (*Figure 2A*). The most common clinical association was new onset atrial fibrillation or flutter (27%), followed by pacemaker implantation with right ventricular pacing (14%). Other noteworthy factors were ventricular arrhythmia, myocardial ischaemia, and cardiac surgery.

The prevalence of the various clinical events preceding HCMr in HCMrb and HCMrf groups is shown in *Figure 2B*. Atrial fibrillation or flutter were commonly documented prior to diagnosing reduced LVEF in HCMrf (n = 16, 35%), while right ventricular pacing was noted in similar rates regardless of the timing of HCMr (n = 5, 15% in HCMrb; n = 7, 14% in HCMrf).

Genetic testing in patients with hypertrophic cardiomyopathy with reduced ventricular function

Among the 83 patients with HCMr, 53 (64%, 17 female and 36 male patients) had undergone some form of genetic testing (*Table S3*). Because of large variability in the extent and technique of testing, we hereby report the *pathogenic* or *likely pathogenic* variants identified in sarcomere protein genes and other established causes of LV hypertrophy (4). Overall, 38 HCMr patients (72% of those tested) had one or more pathogenic genetic variants. Patients with a documented pathogenic genetic variant were younger at HCM diagnosis [26 years (18–44) vs. 50 years (36–60) in no pathogenic variant] and at development of HCMr [51 years (44–59) vs. 67 years (55–75) in no pathogenic genetic variant, $P = 0.008$].

Detailed information on genetically tested patients including age of manifestation and gene variants is provided in *Table S4*.

The most common gene where pathogenic genetic variants were found in HCMr was myosin binding protein C3 (*MYBPC3*; $n = 20$), followed by myosin heavy chain (*MYH7*; $n = 7$) and the thin filaments combined ($n = 8$). There were no notable differences in the age of HCM or HCMr diagnosis, or gender, according to gene.

Six patients had more than one pathogenic genetic variant in the sarcomere genes; one of which was in the *MYPBC3* gene. Four patients had two pathogenic genetic variants in the gene coding *MYBPC3*. Among the 20 patients with *MYBPC3* pathogenic variants, patients with more than one variants were younger at HCM diagnosis [22 years (19–26) vs. 40 years (26–50), $P = 0.01$] and at the diagnosis of HCMr [46 years (42–49) vs. 53 years (50–60), $P = 0.01$]. Finally, six patients carried a mutation previously described as associated with adverse prognosis such as *MYH7* converter region mutations[11] or *TNNT2* p.Glu163del[3] and three had a phenocopy (three with *PKRAG2* syndrome and one with Noonan; *Table S4*).

Table 3 Multivariate regression analysis for development of HCM with reduced ejection fraction

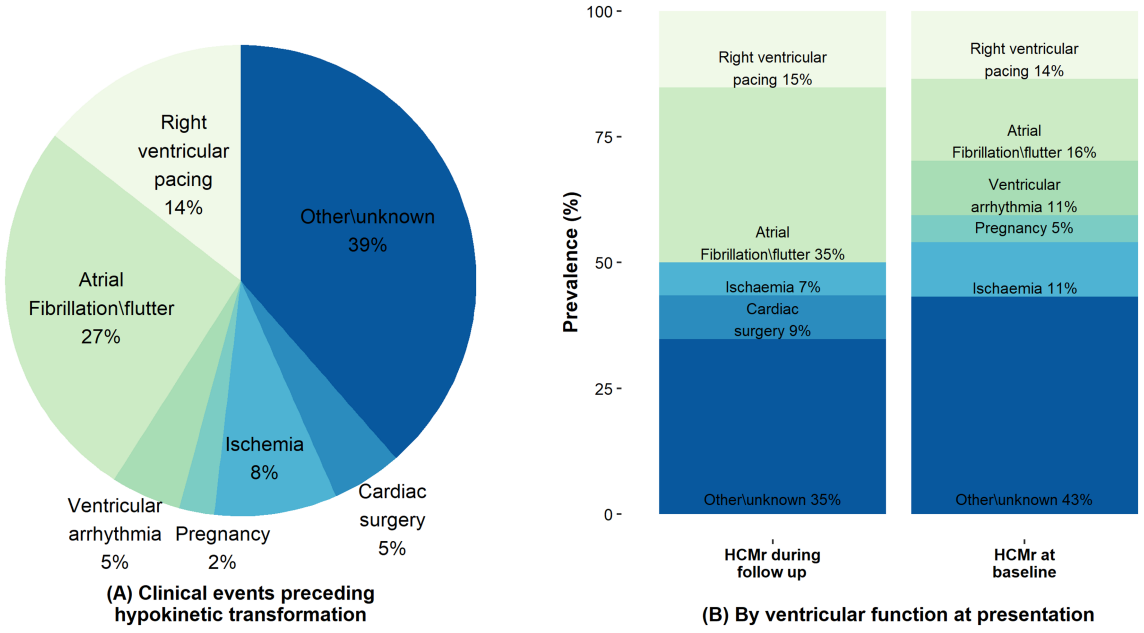
	Adjusted HR	95%CI	*P*
Time from diagnosis ≥ 5 years	1.33	0.7–2.5	0.38
Atrial fibrillation	2.27	1.2–4.2	0.01
Permanent pacemaker	3.67	1.8–7.5	<0.001
LV ejection fraction ≤ 55%	4.58	2.4–8.8	<0.001
Obstructive HCM	0.24	0.1–0.6	0.004
Maximal LV wall thickness ≥ 20 mm	1.61	0.9–2.9	0.13

Risk for development of HCM with reduced ejection fraction during follow up among patients with normal baseline ejection fraction, in a subpopulation matched for age over 60 years, gender, obesity, a personal history of ischaemic heart disease, diabetes mellitus, and chronic kidney disease. Refer to *Methods* section.
CI, confidence interval; HCM, hypertrophic cardiomyopathy; LV, left ventricle.

Outcomes

There were significant differences in the primary outcome of all-cause mortality, ventricular assist device implantation, or

Figure 2 Suspected clinical factors preceding hypokinetic transformation. HCMr, hypertrophic cardiomyopathy with reduced ejection fraction. (*A*) Clinical events preceding the incidence of reduced left ventricular ejection fraction; (*B*) Clinical events according to baseline left ventricular function.



heart transplantation (*Table 4*). Patients with HCMrb were at higher risk for a primary outcome, adjusted for age and gender (HR 7.5, 95%CI 3.1–18, $P < 0.001$, *Figure 3*). HCMrb patients were also at higher risk for both components of the primary endpoint. When comparing the two groups that had a normal baseline LVEF, that is, HCMn vs. HCMrf, no significant differences were seen in neither the composite outcome nor mortality. However, there was a significant risk for ventricular assist device implantation or heart transplantation in the HCMrf group (*Table 4*). A landmark analysis was then performed, comparing the outcomes for HCMrf group adjusted for the time of the first recognition of reduced ejection fraction. The group that developed systolic dysfunction during our follow up (HCMrf) still did better than those had hypokinetic HCM at baseline evaluation, that is, HCMrb (HR 2.52, 95%CI 1.1–5.6, $P = 0.02$).

The Kaplan–Meyer survival estimates from the time of baseline evaluation for the composite outcome according to baseline LVEF is shown in *Figure 3*, with the curves separating early during follow up. The full comparison of the three groups (HCMn, HCMrb, and HCMrf) is provided in *Figure S1*.

Discussion

Hypertrophic cardiomyopathy mostly results in a benign clinical course, with overall survival similar to the general population.[5] Nevertheless, a small subset of patients do develop progressive deterioration of LV systolic function, which may lead to clinically overt heart failure, arrhythmia, and death.[8] In this contemporary cohort, comprising data on patients who presented with HCMr as well as those who developed HCMr in the course of our follow up provide insights about phenotypic characteristics as well as clinical events preceding the diagnosis of HCMr.

Our study compared three groups of patients: those who presented to cardiomyopathy clinic with HCMr, those who presented with normal EF and developed HCMr during follow up, and those who had normal EF during the entire course. Patients with HCMrb had worse clinical, ECG, and echocardiographic parameters, as well as significantly impaired functional and exercise capacities.

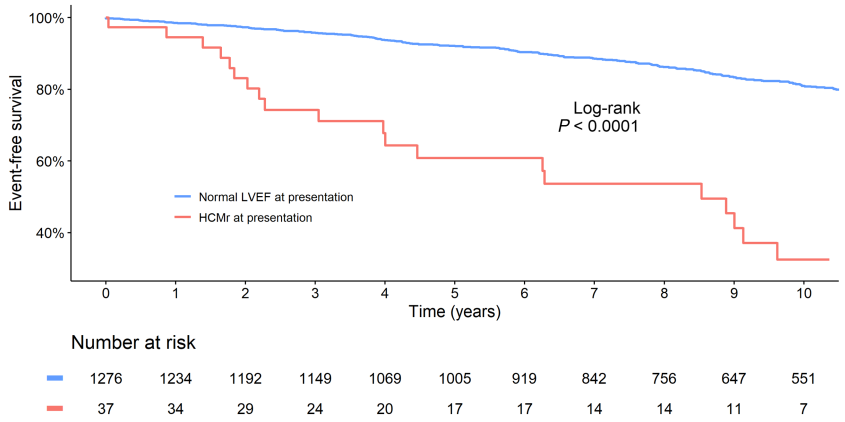
Although most baseline clinical and functional characteristics of patients who developed HCMr during follow up did not differ significantly from HCMn, they had a higher prevalence

Table 4 Outcome analysis in patients with hypokinetic HCM

	HCMn ($n = 1242$)	HCMrf ($n = 46$)	HCMrb ($n = 37$)	HCMrf vs. HCMn			HCMrb vs. normal baseline LVEF		
				Adjusted HR*	95%CI	*P*	Adjusted HR*	95% CI	*P*
Composite outcome	229 (18.6%)	13 (28.3%)	22 (59.5%)	1.3	0.7–2.3	0.35	6.4	4.1–10.1	<0.001
VAD or heart transplant	14 (1.1%)	3 (6.5%)	13 (35.1%)	5.6	1.7–17.9	0.01	87	37.5–202	<0.001
All-cause mortality	219 (17.7%)	10 (21.7%)	11 (21.7%)	1.1	0.6–2.1	0.79	3.2	1.7–6	<0.001

HCMn, patients with hypertrophic cardiomyopathy with normal ejection fraction (at baseline and follow up); HCMrb, hypertrophic cardiomyopathy with reduced ejection fraction developed during follow up; HCMrf, hypertrophic cardiomyopathy with reduced ejection fraction at baseline; LVEF, left ventricular ejection fraction; VAD, ventricular assist device.
Refer to *Methods* section for details.

Figure 3 Composite outcome according to baseline LVEF. HCMr were compared with patients with normal LVEF at baseline. HCMr, hypertrophic cardiomyopathy with reduced ejection fraction; LVEF, left ventricular ejection fraction; Kaplan–Meier survival estimate, showing survival according to baseline left ventricular function.



of intraventricular conduction disturbance, a burden of atrial arrhythmia and NSVT, which led to more ablation and implantable devices procedures. Thus, routine ECG and Holter follow up in HCM should be an effective screening tool to recognize the risk of an impending worsening of LV dysfunction. These patients also had a slightly lower LVEF, well within a normal range, and markedly less obstructive HCM, possibly suggesting an altered contractile reserve.

Nearly all patients with HCMr had a previous documentation of normal systolic function. The proportion of HCMr increased with age (*Figure 1*). As this study was carried out in adult cardiomyopathy clinics, it typically included teenage and adults but not paediatric HCM patients where metabolic cardiomyopathy and hypokinetic transformation is substantially more common.[17]

Our study adds to the body of data regarding HCMr published from two large registries.[6,8] describing the prevalence, complications, and adverse prognosis of HCMr. HCMr was documented in 5–8% of patients, which is similar to the 6.3% seen in our study. The factors predicting the developing hypokinetic HCM are largely unknown but begin to unravel. Early disease onset, multiple, and malignant genetic variants have been associated with hypokinetic transformation and in essence may be described as genetic predisposition. Olivotto *et al*. showed deteriorating systolic function in HCM patients suffering from myocardial perfusion abnormalities.[18] Loss of systolic function is tightly related to myocardial fibrosis, a process that is also linked to wall stiffening and predisposition to cardiac arrhythmia.[19]

The protracted longitudinal design in our study enables description of the course of evolution and clinical events that are associated and may possibly trigger the development of HCMr.[20] Conduction system appears to play a key role in the development of HCMr. This relationship is bidirectional, as arrhythmia can be secondary to ventricular fibrosis or microvascular ischaemia, which may impair LV function, but also cause deterioration through persistent tachycardia. Some of these patients respond poorly to right ventricular pacing, which has previously been used to reduce LV outflow tract gradient,[21] most probably by inducing ventricular asynchrony.[22] Dyssynchronous contraction may be detrimental over time and cause adverse remodelling.[23] In the context of non-obstructive HCM, permanent right ventricular pacing following AV node ablation in 'rapid' atrial fibrillation or due to acquired conduction block may result in deterioration of the systolic function.[24,25] It should be noted that ventricular dimensions at baseline did not differ significantly according to having an implanted device across all subgroups explored in this study. Ventricular dimensions were slightly larger in patients who went on to develop HCMr, both in the matched and unmatched cohorts (*Table 2* and data not shown). This suggests that some of the processes leading to the decline in ventricular function predated device implantation.

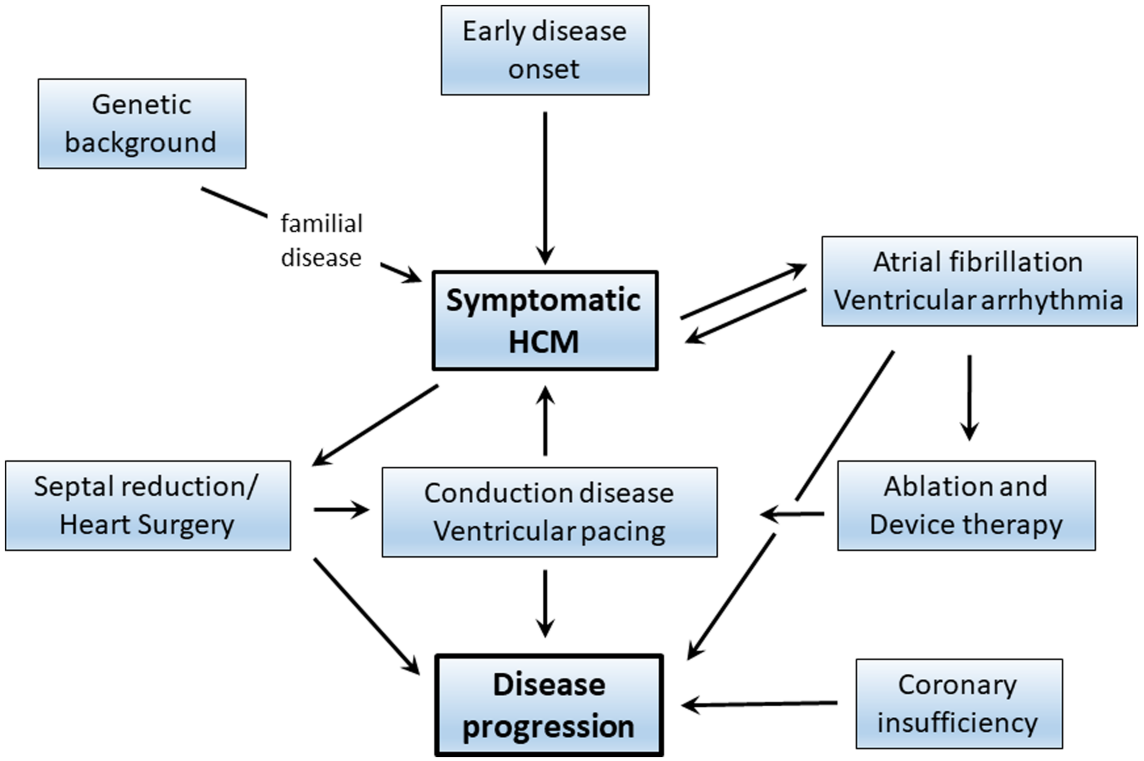
Cardiac ischaemic events and heart surgery preceded development of HCMr in another subgroup (*Table S1* and *Figure 2*). While there were no differences in the prevalence of coronary artery disease or surgical interventions, certain patients may less tolerant to myocardial injury during cardioplegia due to underlying cardiomyopathy.[18] Higher prevalence of prior myectomy in patients with disease progression was already shown in the SHaRe registry, despite lower prevalence of outflow obstruction in this group.[6] This association was unrelated to conduction disturbance and is in line with our observation.

Figure 4 summarizes our emerging understanding of the factors involved in disease progression in HCM based on this study and the available literature. Because no cause and effect relationship has been established, this chart should be viewed as hypothesis generating. HCMr is associated with early onset, longer disease duration, and gene mutations represented by family history of HCM and sudden death. Atrial and ventricular arrhythmia and conduction disease result from the severe phenotype but also have the potential to aggravate it and affect the disease course through irregular rhythm or interventions commencing in right ventricular pacing. These relationships should be explored in properly designed prospective cohorts.

Hypertrophic cardiomyopathy with reduced ejection fraction development may be determined by genetic factors. There are currently over 1500 pathogenic genetic variants that have been associated with HCM, mainly in genes encoding sarcomere proteins.[4] Sarcomere gene pathogenic variants are associated with a younger age of disease onset, greater LV hypertrophy, a more familial disease pattern, and more sudden cardiac death.[12] The combination of early age of disease onset and a recognized sarcomere genetic variant has been associated with poor outcomes in the large contemporary SHaRe Registry.[13]

In our study, the majority of HCMr patients who were genetically tested has a pathogenic variant in a classical 'HCM' gene (*Table S4*). A substantial minority of HCMr patients had two sarcomere mutations including biallelic *MYBPC3* variants. This suggests that for some patients, a two-hit mechanism has a role in disease development and progression. This may explain, at least in part, disparities in the clinical phenotype between different individuals carrying the same genetic variant. Another pathogenic variant, not identified because of inadequate coverage (i.e. gene not included in testing) or in a novel gene, could explain the phenotype in patients with single pathogenic variants or a presumably negative genetic study.[26] A few patients carried genetic variants previously considered 'malignant' such as *MYH7* converter region variants,[11] or in *TNNT2*. There was a remarkable representation of thin filament variants in our HCMr cohort. Classically, *TNNT2* variants were considered to confer a higher arrhythmic risk while *TNNI3* variants were associated with a restrictive phenotype. Our current study

Figure 4 Pathways and factors that may be involved in HCM disease progression. HCM, hypertrophic cardiomyopathy.



suggests that troponin variants may be added to the list of potential causes of hypokinetic transformation. Another fraction of HCM with adverse outcome is explained by metabolic phenocopies such as *PRKAG2* (*Table S3*), Danon's disease[27] or metabolic cardiomyopathy in the paediatric age group.[17] We included these patients in the analysis because they originally presented and were included in this registry as HCM. In our understanding, it is important to recognize them as part of the clinical spectrum of HCM[14] and diagnose them properly because of specific complications including propensity for disease progression.

There are different approaches to genetic testing among patients and their physicians according to age, ethnicity, education, and religion. These factors may lead to selection bias in interpreting the role of genetic findings in HCM disease progression. The approach to gene testing, genetic technology, and testing strategy evolved over time. In our clinical HCMr cohort, there was a sub-optimal 64% testing rate along with heterogeneous methods of testing (rather than a standard panel or whole exome sequencing). Variants of unknown significance in genes such as *TTN* and *FLNC* might have a role in modifying disease course. This obviously limits our ability to draw conclusions and explore various novel potential directions such as modifier genes and effects of the 'variant load'.[16,20,26]

We did not find substantial difference in the age or course of HCMr between the female and male patients although this topic deserves further exploration given the gender differences in HCM features[28] and a lower representation of female patients in our cohort. Diabetes, previously shown to be independently associated with diastolic dysfunction and worse functional status in HCM,[14] did not appear to be associated with systolic dysfunction. This might be due to the low prevalence across subgroups. The effect of diabetes might need more time to manifest. Alternatively, diabetes may have a greater contribution to the other form of disease progression in HCM—the restrictive phenotype.[29]

Cardiomyocyte death and progressive myocardial fibrosis may be considered a final common pathway of structural damage, metabolic derangement, or calcium dysregulation, translating all these adverse changes into systolic and diastolic dysfunction. Fibrosis, unloading and improving the mitochondrial function, should be the prime targets for intervention to prevent disease progression.[30]

As could be expected, patients with HCMr at baseline had worse clinical outcomes while patients who developed HCMr during follow up had better outcome, with mortality rates comparable with the control HCM group with normal LVEF. This might be due to the greater heterogeneity of this group and/or inadequate follow up from onset of HCMr in the

HCMrb group. Notwithstanding these reservations, timely recognition of the change in cardiac condition and modern medical interventions such as classical and newer guideline directed heart failure therapies[31] (i.e. sacubitril/valsartan, empaglifozin, and dapaglifozin) and appropriately used cardiac resynchronization therapy may have a positive impact on the natural history of HCMrf in contemporary cardiomyopathy/heart failure clinic.[32] We therefore believe that a better outcome in HCMrf compared with HCMrb may be attributed to modern management strategies including advanced heart failure therapies (*Figure 3* and *Table 4*).

The use of data from two tertiary referral centres may limit the generalizability of our findings.

Both centres follow the ESC HCM guidelines[4] and may thus represent a different perspective compared with North America, Asia, and so on. This could manifest in different approaches to risk stratification, surgery, and device implantation. However, our results are compatible with those of Maron *et al*.[8] HCMr and in particular HCMrf in our cohort appears to be better than that reported in SHaRe,[6] possibly because ours represents a more contemporary patient population and management strategies.

Limitations

Since patients have been included in the registry for over 20 years, there was heterogeneity in the clinical presentation and management over the years as well as changes in the genetic testing availability and in the technology. The date and age of developing HCMr may not be precise because not all the patients were diagnosed in our centres and indeed some had a protracted course prior to our evaluation. In this clinical HCM cohort with no prospective genetic analysis, we had only 64% testing rate in the HCMr group (and even lower in HCMn group, data not shown) as well as heterogeneous methods of testing, limiting the ability to make comparisons and draw conclusions, and explore potential directions such as modifier genes and effects of the 'variant load'. As genetics obviously plays a role in disease progression, prospective multicentre, multinational studies with standardized genetic and clinical data collection are needed.

Finally, there is no proof of causality between the potential clinical triggers described in *Figures 2* and *4* and the evolution of HCMr, but rather demonstration of clinical associations that warrant awareness and need validation in further studies.

Conclusions

Hypertrophic cardiomyopathy with reduced ejection fraction is associated with poor functional capacity, arrhythmia, and poor outcome. There are several baseline ECG and echocardiographic features that may suggest future development of HCMr. Factors such as bradyarrhythmia and tachyarrhythmia, surgery, and device implantation, were commonly documented close to the time of HCMr development and might be either result or trigger to adverse remodelling. Genetic mechanisms appear to be involved in disease progression: some patients have more than one pathogenic genetic variant, while others carry a malignant gene mutation. Future studies should focus on predictive scores for the development of HCMr, as well as mitigation of potential triggers on the hypertrophic ventricle.

Conflict of interest

The authors have no conflicts to declare.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Composite outcome according to baseline or follow-up compared to HCM who remained with normal LVEF.
HCMn Hypertrophic cardiomyopathy with normal ejection fraction; HCMrb Hypertrophic cardiomyopathy with reduced ejection fraction at baseline; HCMrf Hypertrophic cardiomyopathy with reduced ejection fraction during follow-up; Kaplan–Meier survival estimate, differentiating the 2 subgroups that present as HCMn: those who remained HCMn, and HCMrf.
Table S1. Medical therapy and previous invasive therapy
Categorical variables are described as n (%). See 'methods' section for further clarifications; * Comparing both groups with normal baseline ejection fraction; # Comparing patients by left ventricular function at first evaluation; HCMn HCM with normal ejection fraction; HCMr HCM with reduced ejection fraction; HCM Hypertrophic cardiomyopathy; ACE angiotensin-converting enzyme; ARB angiotensin receptor blocker.
Table S2. Baseline Characteristics of patients with normal ventricular function in a matched cohort.
Categorical variables are described as n (%). Continuous variables are described as median (IQR) or mean (±SD). See 'methods' section for further clarifications; * Comparing both groups with normal baseline ejection fraction; # Comparing patients by left ventricular function at first evaluation; HCMn HCM with normal ejection fraction; HCMr HCM with reduced ejection fraction; HCM Hypertrophic cardiomyopathy; EF

Ejection fraction; COPD Chronic obstructive pulmonary disease; VT Ventricular tachycardia; VF Ventricular fibrillation; SCD Sudden cardiac death.

Table S3. Multivariate Regression analysis for development of HCMr.

Logistic regression as in Table 3 including the country of origin in the analysis. LV Left ventricle; HCM Hypertrophic cardiomyopathy; Risk for development of HCM with reduced ejection fraction during follow-up among patients with normal baseline ejection fraction, in a subpopulation matched for age over 60 years, gender, obesity, a personal history of ischemic heart disease, diabetes mellitus and chronic kidney disease. The effects shown were consistent and independent of the country of origin.

Table S4. Results of genetic testing in patients with reduced ejection fraction.

HCMr, HCM with reduced ejection fraction;

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