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Long-Term Prevalence of Systolic Dysfunction in MYBPC3 Versus MYH7-Related Hypertrophic Cardiomyopathy

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Original Citation:

Long-Term Prevalence of Systolic Dysfunction in MYBPC3 Versus MYH7-Related Hypertrophic Cardiomyopathy / Beltrami, M., Fedele, E., Fumagalli, C., Mazzarotto, F., Girolami, F., Ferrantini, C., Coppini, R., Tofani, L., Bertaccini, B., Poggesi, C., Olivotto, I.. - In: CIRCULATION. - ISSN 2574-8300. - ELETTRONICO. - (2023), pp. 1-9. [10.1161/CIRCGEN.122.003832]

Availability:

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Published version:

DOI: 10.1161/CIRCGEN.122.003832

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07 November 2026

Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

Long-Term Prevalence of Systolic Dysfunction in MYBPC3 Versus MYH7-Related Hypertrophic Cardiomyopathy

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BACKGROUND: The 2 sarcomere genes most commonly associated with hypertrophic cardiomyopathy (HCM), MYBPC3 (myosin-binding protein C3) and MYH7 (β-myosin heavy chain), are indistinguishable at presentation, and genotype-phenotype correlations have been elusive. Based on molecular and pathophysiological differences, however, it is plausible to hypothesize a different behavior in myocardial performance, impacting lifetime changes in left ventricular (LV) function.

METHODS: We reviewed the initial and final echocardiograms of 402 consecutive HCM patients with pathogenic or likely pathogenic MYBPC3 (n=251) or MYH7 (n=151) mutations, followed over 9±8 years.

RESULTS: At presentation, MYBPC3 patients were less frequently obstructive (15% versus 26%; *P*=0.005) and had lower LV ejection fraction compared with MYH7 (66±8% versus 68±8%, respectively; *P*=0.03). Both HCM patients harboring MYBPC3 and MYH7 mutations exhibited a small but significant decline in LV systolic function during follow-up; however, new onset of severe LV systolic dysfunction (LV ejection fraction, <50%) was greater among MYBPC3 patients (15% versus 5% among MYH7; *P*=0.013). Prevalence of grade II/III diastolic dysfunction at final evaluation was comparable between MYBPC3 and MYH7 patients (*P*=0.509). In a Cox multivariable analysis, MYBPC3-positive status (hazard ratio, 2.53 [95% CI, 1.09–5.82]; *P*=0.029), age (hazard ratio, 1.03 [95% CI, 1.00–1.06]; *P*=0.027), and atrial fibrillation (hazard ratio, 2.39 [95% CI, 1.14–5.05]; *P*=0.020) were independent predictors of severe systolic dysfunction. No statistically significant differences occurred with regard to incidence of atrial fibrillation, heart failure, appropriate implanted cardioverter defibrillator shock, or cardiovascular death.

CONCLUSIONS: MYBPC3-related HCM showed increased long-term prevalence of systolic dysfunction compared with MYH7, in spite of similar outcome. Such observations suggest different pathophysiology of clinical progression in the 2 subsets and may prove relevant for understanding of genotype-phenotype correlations in HCM.

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Key Words: cardiomyopathy, hypertrophic ■ incidence ■ mutation ■ stroke volume ■ ventricular dysfunction, left

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Hypertrophic cardiomyopathy (HCM) is the most common heritable heart disease, with heterogeneous clinical profile and outcome. Mutations in the genes encoding MYH7 (β-myosin heavy chain) and MYBPC3 (myosin-binding protein C3) comprise the large majority of genotype-positive HCM patients. MYH7- and MYBPC3-related HCM appear indistinguishable at presentation in terms of phenotype and functional characteristics as assessed by contemporary imaging techniques, and genotype-phenotype correlations have been inconclusive.[1] Nevertheless, there are significant molecular differences between the 2 genes that suggest the possibility of diverse cardiac performance and phenotypic evolution over the long term. Myosin heavy chain is well known to act as the

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCGEN.122.003832.
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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
HCM	hypertrophic cardiomyopathy
HF	heart failure
HR	hazard ratio
LV	left ventricle
LVEF	left ventricular ejection fraction
MYBPC3	myosin-binding protein C3
MYH7	β-myosin heavy chain

molecular motor of the heart, generating force and motion by coupling its ATPase activity to its cyclic interaction with actin. Conversely, the exact role of myosin-binding protein C is unresolved, and its role as a tether to control myosin-actin interaction represents a mere hypothesis.[2] Moreover, pathogenic variants in MYH7 are mainly missense and generate significant amounts of abnormal proteins that is incorporated into the sarcomere, with the potential to exert a poison effect on cardiomyocytes.[3] Conversely, mutations in MYBPC3 are mainly frameshift, causing aberrant splicing, leading to lack of protein production and haplotype insufficiency.[4] Although the mechanism linking haploinsufficiency to HCM development is unresolved, it is assumed that the increased Ca^{+} sensitivity and contractility seen in MYBPC3-HCM lead to energy deficiency and compensatory hypertrophy.[5] Data from cohorts with founder mutations and transgenic animal models suggest the tendency of MYBPC3-HCM to evolve toward long-term systolic impairment, while no such signal is present in MYH7-related disease.[6] We sought to understand whether these important differences might become evident in the long-term evolution of left ventricular (LV) performance, leading to greater age-related decline in LV systolic function and adverse outcome in patients with MYBPC3- compared with MYH7-related HCM.

METHODS

Methods describing the study population, mutational analyses, echocardiography, follow-up, and clinical outcome and statistical analyses are available in the Supplemental Material. The study was approved by an institutional review board, and all patients provided written informed consent. The authors declare that all supporting data are available within the article (and its Supplemental Material).

RESULTS

Baseline Characteristics of MYBPC3 Versus MYH7-HCM

A total of 251 MYBPC3 and 151 MYH7 patients with pathogenic or likely pathogenic variants were included. Patients were diagnosed at a mean age of 39±17 years. Compared with the MYH7-positive cohort, MYBPC3 patients were more often male (68% versus 56%; *P*=0.013) and less frequently obstructive (15% versus 26%; *P*=0.005). Clinical status (New York Heart Association class), maximal LV wall thickness, distribution of LV hypertrophy, and left atrial enlargement did not differ between the 2 genotypes (Table 1).

LV Systolic Function at Initial Evaluation

MYBPC3 patients displayed lower LV ejection fraction (LVEF) compared with MYH7 (66±8% versus 68±8%, respectively; *P*=0.03) and a lower proportion of patients with supernormal systolic function (LVEF, ≥70%; 38% versus 55%; *P*=0.001). Overall, the proportion of patients presenting with severe LV systolic dysfunction (LVEF, ≤50%) was not different between the 2 groups (4% versus 5%; *P*=0.581). However, such patients were more prevalent in the MYBPC3 group versus MYH7 at the age of ≥60 years (*P*=0.017; Figure 1).

Systolic Function at Follow-Up

LV volumes remained stable over time in both genetic groups (MYH7: end diastolic volume index: 51±12 versus 54±13, *P*=0.233; end systolic volume index: 17±6 versus 18±7, *P*=0.074; MYBPC3: end diastolic volume index: 53±15 versus 54±12, *P*=0.106; end systolic volume index: 18±8 versus 19±10, *P*=0.058). Overall, patients developed a limited but significant reduction in LVEF during follow-up (MYBPC3: 61±11% at follow-up versus 66±8% at baseline, *P*<0.001; MYH7: 64±9% at follow-up versus 68±8% at baseline, *P*<0.0001). In addition, MYBPC3 patients showed a lower LVEF at final evaluation compared with MYH7 (61±11% versus 64±9%; *P*=0.01). The prevalence of patients with severe systolic dysfunction (LVEF, ≤50%) was higher among MYBPC3 (15% versus 5%; *P*=0.013). The presence of a MYBPC3 mutation was associated with a higher likelihood of a new onset of LVEF ≤50% at Kaplan-Meyer analysis (*P*=0.040; Figure 2) At Cox multivariable analysis, the presence of a MYBPC3 mutation (hazard ratio [HR], 2.53 [95% CI, 1.09–5.82]; *P*=0.029), older age (HR, 1.03 [95% CI, 1.00–1.06]; *P*=0.027), and atrial fibrillation (AF; HR, 2.39 [95% CI, 1.14–5.05]; *P*=0.021) were independently associated with LVEF ≤50% at the final visit. Among patients with MYBPC3 HCM, the presence of LVEF <50% was similar in patients with and without truncating variants (n=9 or 2.2% versus n=7 or 1.7%; *P*=nonsignificant; Table 2).

Diastolic Function

At baseline, the proportion of patients with diastolic dysfunction grade I, II, and III was similar in the 2 groups

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Table 1. Baseline Clinical and Instrumental Features of the 402 Patients With HCM

	Full HCM cohort (n=402)	MYBPC3 (n=251)	MYH7 (n=151)	*P* value
Protein-truncating variants, %		39.3	0	<0.001
Protein nontruncating variants, %		60.7	100	<0.001
Age at diagnosis, y	39±17	40±17	39±18	0.805*
Sex: male, n (%)	254 (63)	170 (68)	84 (56)	0.013
BSA, m² (mean±SD)	1.9±0.23	1.9±0.22	1.8±0.24	0.328
Family history of SCD	11%	11%	12%	0.811
Age at 1° echocardiography	43±17	43±17	43±18	0.719*
NYHA class, n (%)				0.221
I	241 (60)	161 (64)	80 (53)	
II	127 (31)	72 (29)	55 (36)	
III	32 (8)	16 (6)	16 (11)	
IV	2 (1)	2 (1)	0	
AF, n (%)	81 (20)	53 (21)	28 (19)	0.597
Maximal LVWT, mm (mean±SD)	21±6	21±6	21±6	0.998
LVOT obstruction, n (%)	76 (19)	37 (15)	39 (26)	0.005
Left atrial volume, mL/m² (mean±SD)	43±20	41±18	45±22	0.201*
LVEDV, mL/m² (mean±SD)	52±14	53±15	51±12	0.173*
LVESV, mL/m² (mean±SD)	18±7	18±8	17±6	0.359*
LVEF, % (mean±SD)	67±8	66±8	68±8	0.003
LVEF≤50%, n (%)	16 (4)	9 (4)	7 (5)	0.467
Normal diastolic function, n (%)	105 (34)	69 (36)	36 (30)	0.144
I° grade diastolic dysfunction, n (%)	117 (38)	74 (39)	43 (34)	0.112
II° grade diastolic dysfunction, n (%)	63 (20)	34 (18)	29 (25)	0.132
III° grade diastolic dysfunction, n (%)	23 (7)	13 (7)	10 (9)	0.138
Treatment (time 0)				
β-Blockers, n (%); nadolol equivalent†; median (IQR), mg/d	261 (65) 40 (20–80)	165 (66) 40 (20–80)	98 (65) 60 (20–80)	0.133*
Verapamil/diltiazem, n (%); median (IQR), mg/d	52 (13) 120 (80–240)	32 (13) 120 (80–240)	21 (14) 120 (80–240)	0.999*
Disopyramide, n (%); median (IQR), mg/d	4 (1) 250 (125–500)	2 (1) 250 (125–500)	3 (2) 250 (125–500)	0.992*
ACE inhibitor/ARB, n (%); ramipril equivalent‡; median (IQR), mg/d	56 (14) 5 (2.5–10)	37 (15) 7.5 (2.5–10)	21 (14) 5 (2.5–10)	0.999*

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BSA, body surface area; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness; MYBPC3, myosin-binding protein C3; MYH7, β-myosin heavy chain; NYHA, New York Heart Association; and SCD, sudden cardiac death.

*P value calculated with nonparametric test (Mann-Whitney *U* test).

†Median dose and IQR of patients receiving the drug: nadolol, 80 mg; metoprolol, 100 mg; propranolol, 80 mg; bisoprolol, 5 mg; atenolol, 50 mg.

‡Ramipril, 10 mg; enalapril, 20 mg; lisinopril, 20 mg. References are provided in the Supplemental Material.

(Table 1). In MYBPC3 patients, diastolic function tended to worsen with age (*P*=0.01). Among patients aged <20 years, prevalence of advanced diastolic dysfunction was higher in MYH7 compared with MYBPC3 patients (*P*=0.007; Figure 3A).

At follow-up, the incidence of grade II/III diastolic dysfunction increased with age among MYBPC3 but not among MYH7 patients (*P*=0.023). Overall, there was no statistically significant difference occurred in diastolic dysfunction grade II/III between MYBPC3 and MYH7 by age groups at final visit (Figure 3B). At Cox multivariable analysis, LV outflow obstruction (HR, 2.77 [95% CI, 1.47–5.20]; *P*=0.002) and older age (HR, 1.02 [95% CI, 1.00–1.03]; *P*=0.024) were the only predictors of diastolic dysfunction at follow-up.

LA size increased significantly in both groups; both the magnitude and rate of remodeling were again similar for both groups. Notably, there was no statistically significant difference in LA size at baseline between MYH7 and MYBPC3, and no interaction was noted between LAVi at baseline and genotype (*P* value for Wald, 0.245). Over follow-up LAVi increased, with an annual rate of 0.8 (0.6–1.1) mL/m² per year, comparable in both groups (overall *P*=0.23); in MYH7, from 45±22 to 55±27 mL/m², *P*<0.001; in MYBPC3: from 41±18 to 49±28 mL/m², *P*<0.001. Overall, higher baseline values of LAVi correlated with higher risk of AF, as expected (*P*<0.001).

Long-Term Outcome

At a mean follow-up of 9±8 years, no significant differences were observed between MYBPC3 and MYH7 patients in terms of symptoms severity (New York Heart Association class III, *P*=0.7; New York Heart Association class IV, *P*=0.6), incidence of AF (*P*=0.4), stroke (*P*=0.9), heart failure (HF) hospitalization (*P*=0.9), cardiac arrest (*P*=0.09), and cardiovascular death (*P*=0.2; Table 3).

However, the prevalence of nonsustained ventricular tachycardia was higher in the MYBPC3-positive patients (39% versus 14%; *P*<0.0001). In our cohort, we did not have any occurrence of slow sustained ventricular tachycardia below the detection threshold of the device. A total of 4.2% of patients with implantable cardioverter defibrillator had appropriate ATP, while 14.5% of patients with implantable cardioverter defibrillator experienced ≥1 inappropriate shocks mostly due to AF.

DISCUSSION

In the present study, both HCM patients harboring MYBPC3 and MYH7 mutations exhibited a small but significant decline in LV systolic function during follow-up; however, while the mean reduction was similar among

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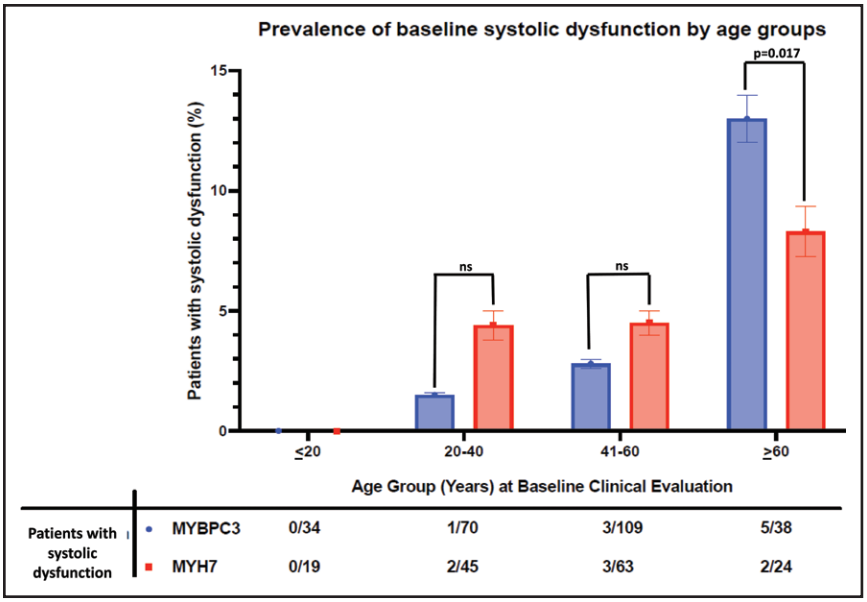

Figure 1. Prevalence of left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF], ≤50%) by age groups in MYBPC3 (myosin-binding protein C3) versus MYH7 (β-myosin heavy chain).

the 2 groups (−5% versus −4%), new onset of severe LV systolic dysfunction (LVEF, ≤50%) was greater among MYBPC3 patients (15%, versus 5% among MYH7; *P*=0.013). Notably, MYBPC3-positive status proved an independent predictor of severe systolic dysfunction, together with age and AF, at multivariable analysis. Data from the SHARE registry demonstrated that greater LV cavity size, greater LV wall thickness, and the presence of a pathogenic/likely pathogenic sarcomeric variant were associated with increased risk of incident LV systolic dysfunction in HCM.[7] The significant higher prevalence of LV systolic dysfunction in the MYBPC3 group (which occurred in similar proportions among patients with and without truncating variants) points out the different

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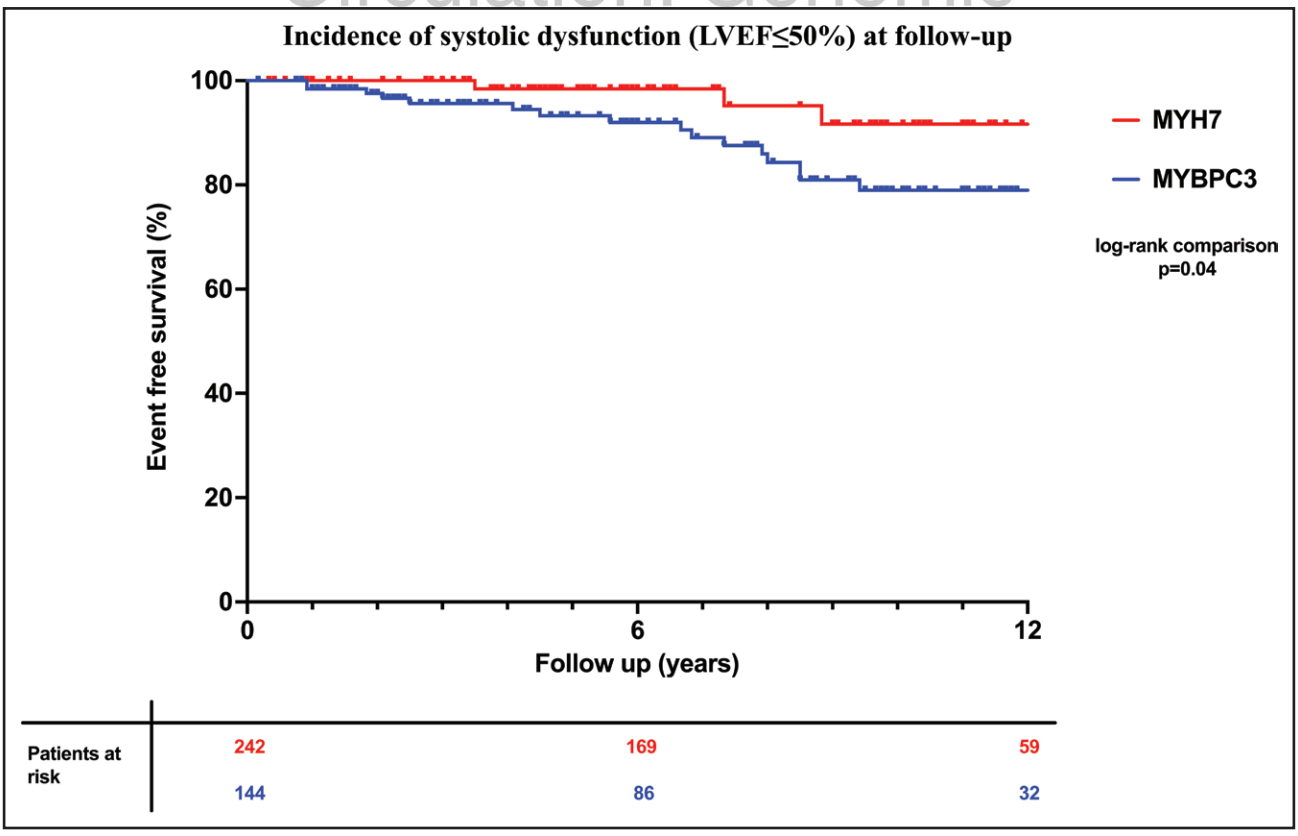

Figure 2. Kaplan-Meier analyses for severe systolic dysfunction at follow-up (left ventricular ejection fraction [LVEF], ≤50%). MYBPC3 indicates myosin-binding protein C3; and MYH7, β-myosin heavy chain.

Table 2. Cox Multivariable Regression Analysis for Factors Associated With LVEF ≤50% at the Final Visit

Variables	Univariate HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Genotype (MYBPC3 vs MYH7)	3.11 (1.71–9.66)	0.018	2.53 (1.09–5.82)	0.029
Age, y	1.04 (1.00–1.09)	0.049	1.03 (1.00–1.06)	0.027
AF	2.87 (1.56–7.11)	0.034	2.39 (1.14–5.05)	0.021
Gender (women vs men)	1.53 (0.72–3.78)	0.201	…	…
MYBPC3 nontruncating variants	1.06 (0.83–2.01)	0.199	…	…
NSVT	1.04 (0.88–2.28)	0.194	…	…
HOCM	0.89 (0.29–3.34)	0.620	…	…
NYHA at baseline	1.60 (0.78–2.67)	0.399	…	…
β-Blockers*	0.82 (0.75–1.22)	0.542	…	…
Dose equivalent nadolol ≥40 mg	0.88 (0.65–1.11)	0.495	…	…
Maximal LVWT	2.13 (1.61–8.54)	0.012	2.34 (0.82–4.93)	0.299
Posterior LV wall thickness	3.11 (1.71–9.66)	0.031	2.53 (0.85–5.82)	0.174
BSA	1.02 (0.80–2.11)	0.822	…	…
Family history of SCD	1.04 (0.69–1.09)	0.099	1.01 (0.71–1.39)	0.510
Left atrial volume	1.53 (0.72–3.78)	0.254	…	…
Diastolic dysfunction grade II	2.87 (1.56–7.11)	0.029	2.39 (0.77–5.05)	0.198
Diastolic dysfunction grade III	1.04 (0.88–2.28)	0.210	…	…

AF indicates atrial fibrillation; BSA, body surface area; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; LV, left ventricle; LVWT, left ventricular wall thickness; NSVT, nonsustained ventricular tachycardia; MYBPC3, myosin-binding protein C3; MYH7, β-myosin heavy chain; NYHA, New York Heart Association; and SCD, sudden cardiac death.

*Dose equivalent nadolol, 80 mg; metoprolol, 100 mg; propranolol, 80 mg; bisoprolol, 5 mg; atenolol, 50 mg.

pathophysiological behavior of the 2 most common gene mutations in HCM. Notably, the prevalence of AF was similar in the 2 groups, so that the worse systolic performance of MYBPC3 patients was not explained by an excess of the arrhythmia. Moreover, in MYBPC3 patients, diastolic function tended to worsen with age; thus, the severity of diastolic dysfunction at the final evaluation was comparable between MYBPC3 versus MYH7 patients. No statistically significant differences occurred with regard to the incidence of AF, stroke, HF hospitalization, appropriate implantable cardioverter defibrillator shock, or cardiovascular death. Notably, MYBPC3 and MYH7 patients were phenotypically indistinguishable at baseline, except for a higher male proportion in the MYBPC3 group, in agreement with the existing literature.[8,9] Specifically, MYBPC3-associated phenotypes did not differ from MYH7 with respect to age at diagnosis, degree of hypertrophy, incidence of myectomy, or family history of HCM or sudden death. These findings suggest that, despite considerable individual variations, the 2 main sarcomeric types of HCM reach common clinical destinations through different metabolic and pathophysiological pathways, due to the diverse molecular underpinnings of MYBPC3 and MYH7 mutations. Understanding these nuances may be instrumental to improve our, as yet elusive, perception on genotype-phenotype correlations in HCM.

It is well established that sarcomere$^+$ HCM patients (irrespective of the myofilament involved) have greater risk of long-term impairment in LV function and adverse outcome compared with sarcomere$^-$ patients, while patients with variants of uncertain significance have an intermediate prognosis.[10] Sarcomere$^+$ patients more often have reverse septal curvature morphology and myocardial fibrosis compared with sarcomere$^-$ patients, but to date, differences between MYBPC3 and MYH7-associated HCM remain elusive. More specifically, for example, CMR studies report similar degrees of LVH, prevalence and burden of myocardial fibrosis, and T1 mapping profiles.[11] With regard to clinical features, certain authors demonstrated incomplete penetrance, delayed presentation, and favorable clinical course of MYBPC3 mutations in comparison to MYH7.[12] However, other studies emphasized more extensive hypertrophy and worse outcome in carriers of specific MYBPC3 disease-causing variants, more frequently progressing toward LV systolic dysfunction.[13,14] Weissler-Snir et al[15] showed that MYBPC3 gene mutations were associated with a significantly lower LVEF than MYH7 gene mutations in patients ≥40 years of age. In a multicenter study, mutations in MYBPC3 were more frequently associated with end-stage HCM compared with MYH7.[16]

In a broader perspective, MYBPC3 is a gene potentially predisposing to LV systolic dysfunction. Myosin-binding protein C is a regulatory protein located in the A band of the cardiac sarcomere, providing mechanical stability,[17] influencing the force activation across the sarcomere, and modulating systolic stiffening.[18] The majority of pathogenic MYBPC3 variants are premature stop codons or frameshift mutations found in heterozygosity, frequently associated with the lack of 50% of the wild-type protein. The majority of MYBPC3 patients have stop codons leading production of truncating protein, which is removed by cellular autophagy, causing haplotype insufficiency whereas in MYH7-related disease mutations causing a poison peptide effect. The transgenic mouse model developed by the Carrier group, carrying a pathogenic HCM-associated variant, is characterized by the heterozygous animal showing only mild disease features and by the homozygous mouse developing severe hypokinetic dilated cardiomyopathy.[19] In humans, MYBPC3 variations seem to predispose to acquired LV dysfunction. Harper et al[20] reported an increased risk of HF associated with a common MYBPC3 mutation present in

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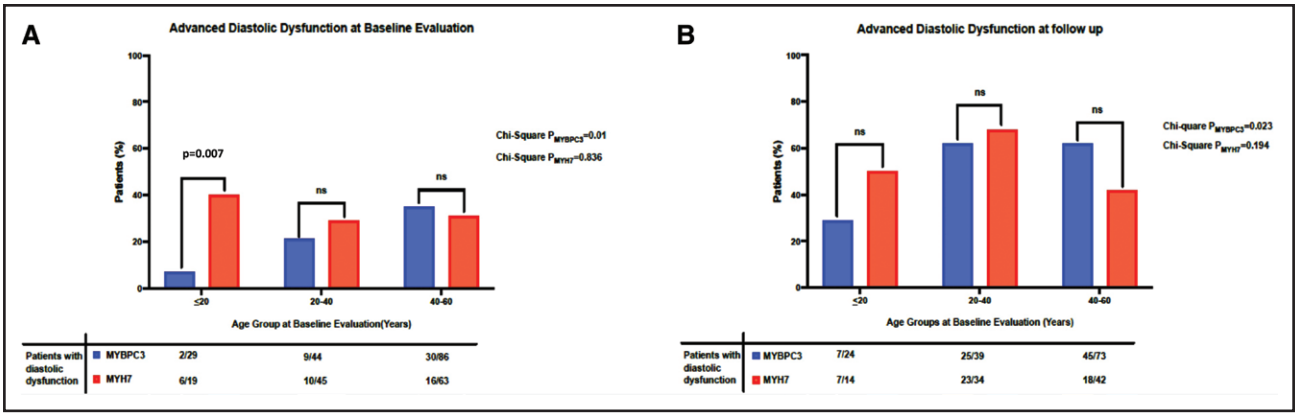

Figure 3. Advanced diastolic dysfunction by genetic status at baseline and follow-up.
Data presented refer to the prevalence (**A**) and incidence (**B**) of diastolic dysfunction by age groups at diagnosis in patients with MYBPC3 (myosin-binding protein C3) and MYH7 (β-myosin heavy chain) mutations. In both panels, age groups refer to the age at first clinical evaluation (ie, the first visit). The association between the presence of advanced diastolic dysfunction and age classes in MYBPC3 patients, between the presence of advanced diastolic dysfunction and age classes in MYH7 patients and between the presence of advanced diastolic and gene mutation within each age classes separately were performed with the χ^2 test.

South Asian populations. Furthermore, MYBPC3 mutations appear to increase susceptibility to LV dysfunction in patients with coronary artery disease.[21] In light of these findings, the hypothesis that MYBPC3 predisposes to age-related decline in systolic function is plausible. In HCM, the recognition of this phenomenon may be hindered by the hypercontractile status present in the early phases of disease, an enhanced systolic reserve may be postulated in these patients, which in most cases prevents LVEF decline from falling below 50%. Conversely, no such signal is seen in MYH7 patients, in whom it is the diastolic dysfunction that dominates at any age, while systolic decline is rare and generally subtended by severe fibrosis rather than by contractile impairment,[22] suggesting a more prominent role for biological senescence, microvascular dysfunction, and abnormal collagen production, in a manner reminiscent of certain phenotypes characterized by HF with preserved ejection fraction.[23]

At the molecular level, many gaps in knowledge persist as to why the natural history of MYBPC3 and MYH7 may diverge over time. Indeed, the 2 genotypes seem to cause similar metabolic and energetic consequences in the myocardium, albeit by different mechanisms (haplotype insufficiency in MYBPC3, dominant negative effect in MYH7). This is supported by recent data showing similar proteomic profiles in HCM patients irrespective of the genotype.[24,25] However, it has been a recurrent observation in our clinic that HCM patients evolving toward systolic dysfunction are more common in the MYBPC3 group. While a definite explanation for this imbalance is lacking, the role of age-related changes has been called into play, including a progressive failure of the nonsense mRNA degradation or of the cardiomyocyte proteolytic systems (ubiquitine proteasome, autophagy) in effectively removing the mutant mRNA and the truncated protein from the cardiomyocyte. By such theory, a quota of poison effect will superimpose to the initial haplotype insufficiency, potentially causing the decline in cardiac function (Carrier et al). Such mechanisms would not impact MYH7 disease, in which the mutant protein is incorporated in the sarcomere from the beginning. The failure of cellular autophagy accumulation of poison peptides might be relevant during aging, in line with the age-related systolic dysfunction in MYBPC3 mutant patients. Moreover, MYBPC3 mutations impair sarcomere energetics, cause loss of crossbridge cycling inhibition, and lead to deranged phosphorylation of contractile proteins and reduced maximal force-generating capacity.[26] HCM abnormalities in substrate metabolism are demonstrated by the reduced phosphocreatine to adenosine triphosphate concentration ratio on phosphorus magnetic resonance spectroscopy is a marker of abnormal energy utilization, which, however, is not unique to MYBPC3.[27] Impaired energetics and perfusion reserve are possible mechanistic drivers of the fibrotic process, which in turn lead to adverse cardiac remodeling, HF progression, and arrhythmia.[28] All in all, MYBPC3 mutations may lead to the progressive disruption of myocyte function by multiple mechanisms and account for the observed propensity toward LV systolic dysfunction.[29]

Building knowledge on the different underlying molecular mechanisms of disease progression in various forms of HCM may be instrumental in tailoring long-term preventive strategies with existing pharmacological options, as well as in indicating novel targets for drug development. Progressive HF associated with LV remodeling and systolic-diastolic dysfunction is one of the most severe complications of HCM. During the last decade, we have begun to understand the mechanisms underlying progression from a hyperdynamic LV to the striking patterns of end-stage disease. To date, different aspects

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Table 3. Clinical and Outcome Characteristics at Follow-Up Between MYBPC3 vs MYH7 Patients

	Total population (N=402)	MYBPC3 (n=251)	MYH7 (n=151)	*P* value
Mean follow-up, y	9±8	9±7	9±9	0.999*
Treatment (last follow-up)				
β-Blockers, n (%); nadolol equivalent†; median (IQR), mg/d	325 (81); 60 (20–80)	205 (82); 60 (20–80)	120 (80); 80 (20–80)	0.101*
Verapamil/diltiazem, n (%); median (IQR), mg/d	44 (11); 240 (80–480)	20 (8); 240 (80–480)	13 (9); 240 (80–480)	0.990*
Disopyramide, n (%); median (IQR), mg/d	44 (11); 500 (250–750)	25 (10); 500 (250–750)	18 (12); 500 (250–750)	0.999*
ACE inhibitor/ ARB, n (%); ramipril equivalent‡; median (IQR), mg/d	(68) 17; 5 (2.5–10)	42 (17); 7.5 (2.5–10)	27 (18); 5 (2.5–10)	0.724*
NYHA class III, n (%)	43 (14)	28 (15)	15 (12)	0.329
NYHA class IV, n (%)	7 (2)	4 (2)	3 (2)	0.532
AF, n (%)	126 (31)	78 (31)	48 (32)	0.405
Stroke, n (%)	22 (5)	15 (6)	7 (5)	0.730
NSVT, n (%)	119 (30)	98 (39)	21 (14)	<0.001
HF hospitalization, n (%)	32 (7)	22 (9)	10 (7)	0.521
ICD, n (%)	85 (21)	57 (23)	28 (19)	0.299
Defibrillator shock, n (%)	14 (3)	12 (5)	2 (1)	0.517
Cardiac arrest, n (%)	11 (3)	9 (4)	2 (1)	0.255
Myectomy, n (%)	54 (13)	30 (12)	24 (16)	0.188
Alcohol septal ablation, n (%)	29 (6)	17 (7)	12 (8)	0.234
Cardiovascular death, n (%)	43 (8)	32 (13)	11 (7)	0.086

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NSVT, nonsustained ventricular tachycardia; MYBPC3, myosin-binding protein C3; MYH7, β-myosin heavy chain; and NYHA, New York Heart Association.

**P* value calculated with nonparametric test (Mann-Whitney *U* test).

†Nadolol, 80 mg; metoprolol, 100 mg; propranolol, 80 mg; 6 bisoprolol, 5 mg; atenolol, 50 mg.

‡Ramipril, 10 mg; enalapril, 20 mg; lisinopril, 20 mg. References are provided in the Supplemental Material.

of HCM progression remain obscure, including potential strategies for management and prevention. On the basis of recent evidence, it is appropriate to emphasize these aspects, which may be difficult to identify, particularly in the early stages when systolic function appears relatively preserved. Nevertheless, it is at these early stages that treatment may potentially interfere with the clinical evolution of HCM toward an end-stage phenotype and HF. Adequately dosed β-blockers have been suggested to provide long-term survival benefit in patients with HCM.[30] Benefits of the β-blocker therapy are particularly evident in obstructive patients, as shown recently in a small randomized trial with metoprolol, which was associated with LVOT-gradient reduction, symptom relief, and lower troponin T serum levels compared with placebo, suggesting myocardial protection.[31] In our study, the percentage of patients using β-blockers was comparable in the 2 groups, and pharmacological treatment in general does not seem to have represented a bias for the evaluation of systolic function. However, the dose range used in our population was lower than doses that have been found to provide long-term survival benefit or reduction in troponin T release in HCM patients with obstruction.[32,33] Nevertheless, we acknowledge that a potential impact of concomitant drug regimens on our findings cannot be excluded due to the retrospective nature of the study.

Recently, allosteric reversible cardiac myosin inhibitors have been developed for HCM, with promising results for relief of obstruction and a potential for disease modification. Mavacamten is not solely to treat obstruction but, rather, as an attempt to address the core mechanisms of HCM at the sarcomere level.[34] Preclinical studies suggest that Mavacamten reverts the primary myofilament abnormalities determined by MYBPC3 haploinsufficiency in models of MYBPC3-mutant HCM.[35] Nonetheless, the benefits on disease progression appear to be less relevant than those observed in models carrying myosin mutations.[36] Based on our findings, symptomatic and functional response of these agents will need to be assessed carefully in the long term with regard to genotype, particularly in MYBPC3 patients, so that the benefit is maximized in the early, hypercontractile stages, and harm is prevented later on, when systolic function is in decline. Whether an early use of myosin inhibitors may prevent disease progression, and whether their effects vary with genotypes, is as yet unknown.

Limitations

This is a retrospective study that did not allow the inference of causal relationships. The cohort did not differ in terms of baseline clinical characteristics, but the study was limited by small numbers of events, despite being recruited from a large expert center. Doppler echocardiographic measures of diastolic function and their existing discrepancies create significant limitation; moreover, we did not have correlation with hemodynamic data of left atrial pressure. Unfortunately, to collect the necessary information in a large number of patients over many years, we unavoidably had to include older echocardiograms and, therefore, could not benefit from systematic data based on novel technologies (speckle-tracking echocardiography). Global longitudinal strain is interesting to evaluate minor degrees of LV systolic dysfunction that may be missed by LVEF alone. Further investigation assessing the long-term progression of LV systolic dysfunction based on genotype still remains mandatory.

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Conclusions

MYBPC3-related HCM shows increased long-term prevalence of systolic dysfunction compared with MYH7, in spite of similar outcome. Such observations suggest different pathophysiology of clinical progression in the 2 HCM subsets and may prove relevant for the understanding of genotype-phenotype correlations in HCM. Furthermore, differences in lifetime myocardial performance between the 2 most common HCM-associated genes may help understanding mechanisms of progression and tailor long-term preventive strategies for this complex disease.

ARTICLE INFORMATION

Received May 18, 2022; accepted May 30, 2023.

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Acknowledgments

The authors wish to acknowledge the valuable help of Katia Baldini and Alessia Tomberli for their effort in the project and continuous long-term care of patients with hypertrophic cardiomyopathy.

Sources of Funding

Dr Olivotto is supported by the European Union Horizon Research and Innovation Programme under grant agreement number 101080905 STRATIFYHF–HORIZON-HLTH-2022-STAYHLTH-01-two-stage. Dr Coppini was supported by the Italian Ministry of University and Research under PRIN grant RHYTHM-INSIGHT and by Fondo di Beneficienza Intesa Sanpaolo.

Disclosures

Dr Olivotto has received research grants from and has served on the advisory board for BMS, Cytokinetics, Amicus, Genzyme, Shire Takeda, Tenaya, Rocket Pharma, and Chiesi. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Figure S1
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