Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy

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Abstract

Background: Severe left ventricular (LV) systolic dysfunction is an uncommon complication of hypertrophic cardiomyopathy (HCM) that is associated with poor prognosis. Small observational series suggest that patients with rare causes of HCM are more likely to develop systolic impairment than those with idiopathic disease or mutations in cardiac sarcomeric protein genes. The aim of this study was to test this hypothesis by comparing the prevalence of systolic dysfunction and its impact on prognosis in patients with different causes of HCM.

Methods and Results: 1697 patients [52 (40-63) years, 1160 (68%) males] with HCM followed at two European referral centres were studied. Diagnosis of specific aetiologies was made on the basis of clinical examination, cardiac imaging and targeted genetic and biochemical testing. The primary survival outcome was all-cause mortality or heart transplantation (HTx) for end-stage heart failure. Secondary outcomes were heart failure (HF)-related death, sudden cardiac death, stroke-related death, and non-cardiovascular (CV) death.

Systolic dysfunction (LV ejection fraction <50% by 2D-echocardiography) at first evaluation was more frequent in rare phenocopies than in idiopathic or sarcomeric HCM [105/409 (26%) versus 40/1288 (3%), respectively ($p<0.0001$)]. All-cause death/HTx and HF-related death was more frequent in rare phenocopies compared to idiopathic or sarcomeric HCM, ($p<0.0001$). All-cause mortality and HF-related death was highest in patients with cardiac amyloidosis, ($p<0.0001$).

Conclusions: In adults with HCM, LV systolic dysfunction is more frequent in those with rare phenocopies. When combined with age at presentation, it is a marker for specific aetiologies and is associated with poorer long-term survival.

What is already known about this subject?

Hypertrophic cardiomyopathy (HCM) is a generic term that encompasses a number of different diseases. Left ventricular (LV) systolic dysfunction is an uncommon complication of the disease, but its relation to underlying aetiology has not been investigated. Similarly, there are no studies in literature investigating the impact of aetiology on long term prognosis in large populations of patients with HCM.

What does this study add?

This study shows that LV systolic dysfunction at first evaluation is more frequent in rare HCM phenocopies than in disease caused by mutations in cardiac sarcomeric protein gene mutations (the commonest cause of HCM). The causes of systolic LV dysfunction varied with age in that there was a higher prevalence of syndromic and metabolic diseases in the young, whereas cardiac amyloidosis was exclusively seen in older age groups. The underlying aetiology also influenced survival with rare phenocopies–in particular cardiac amyloidosis–being associated with a poor long-term survival.

How might this impact on clinical practice?

These findings show that systolic LV dysfunction in patients with HCM is a diagnostic clue that should prompt a systematic search for rarer phenocopies informed by the age of the patient at first presentation. These rare conditions are important because they have prognostic implications and can be overlooked or misdiagnosed if the index of clinical suspicion is low.

Hypertrophic cardiomyopathy (HCM) is a common cardiac disease caused by a number of genetic and acquired disorders [1]. Mutations in genes coding for cardiac sarcomeric proteins account for the majority of cases, but other diseases including inherited disorders of metabolism, myocardial infiltration, neuromuscular disorders and malformation syndromes can present with a similar phenotype. In many cases, obvious clinical features suggest the diagnosis of these less common disorders, but in some patients they may be overlooked or misdiagnosed if the index of clinical suspicion is low.

Severe left ventricular (LV) systolic dysfunction, commonly referred to as end-stage disease or the "burnt-out phase", is an uncommon but important evolution of idiopathic or sarcomeric HCM [2-5]. In tertiary referral centres, end-stage disease has a prevalence of 2-5% and an incidence of 0.5-1 cases per 100 patient years and is associated with a poor prognosis due to high rates of refractory heart failure and sudden arrhythmic death [3-7]. Small observational series suggest that patients with some of the rarer HCM phenocopies are more likely to develop systolic impairment than those with disease caused by sarcomeric protein gene mutations [8-12] and current ESC guidelines suggest that LV systolic dysfunction is one of several clinical features that assist in the differential diagnosis of HCM [13]. The aim of this study was to test this hypothesis by comparing the prevalence of systolic dysfunction in patients with different causes of HCM. A secondary aim was to assess the impact of aetiology on long-term survival.

METHODS

Study design and setting

This was a retrospective, longitudinal cohort study involving patients from two European cardiomyopathy centres – The Heart Hospital, University College Hospitals Trust, London U.K. and Bologna University Hospital, Italy. The study conformed to the principles of the Helsinki declaration.

Study population and patient assessment

Patients were identified by systematically searching hospital records and clinical databases. Patients were evaluated using medical history, pedigree analysis, physical examination, ECG, cardiac imaging and laboratory testing. Further specialised tests such as skeletal muscle and endomyocardial biopsy, and molecular genetic testing were performed when there were features from the pedigree analysis, clinical examination or preliminary investigations that suggested a possible rare phenocopy.

All patients included in the study were ≥16 years of age. HCM was defined as a maximal LV wall thickness (MWT) ≥15 mm or ≥13mm in patients with unequivocal familial disease [14] and/or a diagnosed rare non-sarcomeric phenocopy.

The Heart Hospital population comprised a cohort of unrelated consecutive patients with idiopathic or sarcomeric HCM who were tested for sarcomeric protein gene mutations using high-throughput sequencing between 2011 and 2013 [15] and all patients diagnosed with one of the following conditions between 1991 and 2014: Anderson-Fabry disease (AFD), primary mitochondrial disease, immunoglobulin light chain amyloidosis (AL), hereditary transthyretin type amyloidosis (ATTR), wild-type or senile systemic amyloidosis (SSA), Noonan syndrome, LEOPARD syndrome (Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, Deafness), carnitine palmitoyltransferase II (CPT II) deficiency, mutations in the four and a half LIM domain protein 1

(FHL1) gene, Friedreich's ataxia and glycogen storage disease (GSD) including Danon disease and AMP-protein kinase deficiency caused by mutations in PRKAG2.

The cohort from Bologna University Hospital comprised consecutive patients with idiopathic or sarcomeric HCM (some of whom have been included in other recently published studies) [16-19] and with the same phenocopies as described above assessed between 1980 and 2013.

Data collection

Data were collected independently at each participating centre using uniform methodology. Clinical characteristics were assessed at first (baseline) evaluation. LV systolic dysfunction was defined as a resting LV ejection fraction <50% measured using 2D echocardiography and the biplane Simpson method [5].

Study outcomes

The primary outcome was all-cause mortality or heart transplantation (HTx) for end-stage heart failure. Secondary outcomes were as follows: sudden cardiac death, heart failure (HF)-related death, stroke-related death, and non-cardiovascular (CV) death. When the cause of death was not known, the death was considered non-cardiac in all analyses [20]. The cause of death was ascertained at each centre using hospital and primary health care records, death certificates, post-mortem reports, and interviews with witnesses.

Sudden cardiac death was defined as natural death due to cardiac causes, occurring within 1 hour of the onset of acute symptoms. Death was also classified as sudden if it occurred unexpectedly but was unwitnessed, such as in bed overnight. Appropriate implantable cardioverter–defibrillator (ICD) intervention for ventricular fibrillation or ventricular tachycardia

and aborted cardiac death with successful cardiac resuscitation were considered as equivalent to sudden cardiac death. Heart failure-related death included deaths in individuals with symptoms of progressive heart failure including cardiogenic shock [20].

Statistical analysis

Data are reported as median and interquartile range (IQR) for continuous variables or frequencies (percentage) for categorical variables. Comparison of clinical and laboratory variables between patient subgroups was performed with 2-sample t-test for continuous parametric variables and Mann–Whitney U test for all continuous non-parametric variables. Categorical variables were compared using Chi-square test for parametric data. Comparisons of multiple groups of continuous non-parametric data were performed using the Kruskall Wallis test.

The follow-up time for each patient was calculated from the date of their first evaluation at each centre to the date of the primary end-point or to the date of their most recent clinical evaluation. The cumulative probability for the occurrence of an outcome was estimated using the Kaplan-Meier method and log-rank test from the first clinical evaluation at the referral centre.

All p-values were two-sided and the results were considered statistically significant if < 0.05. SPSS (Version 22.0) was used for all statistical analyses.

RESULTS

The combined study population consisted of 1703 patients. Six patients were excluded as there were no verifiable data on LV systolic function. Eight seven per cent of the entire cohort had a wall thickness ≥15 mm. Of the remainder, 7% had a family history of HCM caused by a sarcomeric protein gene mutation and 6% had rare phenocopies; 74% (304/409) of the phencopies had MWT

≥15mm. Figure 1 shows the patient population selection process and Table 1 summarizes the different aetiological subgroups at each centre.

Table 1. Summary of diagnostic subgroups at each centre.

	Overall n=1697	**The Heart Hospital** n=987 (58%)	**Bologna University Hospital** n=710 (42%)
Idiopathic or sarcomeric HCM n (%)	1288 (76)	826 (49)	462 (27)
Phenocopies, n (%)	409 (24)	161 (9)	248 (15)
AL amyloidosis, n (%)	115 (7)	6 (0.4)	109 (6)
Hereditary TTR amyloidosis, n (%)	86 (5)	6 (0.4)	80 (5)
Anderson-Fabry disease (AFD), n (%)	85 (5)	77 (5)	8 (0.5)
Wild-type or SSA, n (%)	48 (3)	8 (0.5)	40 (2)
Noonan syndrome, n (%)	15 (1)	11 (0.6)	4 (0.2)
Mitochondrial diseases, n (%)	23 (1)	21 (1)	2 (0.1)
Friedreich's ataxia, n (%)	11 (1)	9 (0.5)	2 (0.1)
Glycogen storage disease (GSD), n (%)	16 (1)	14 (0.8)	2 (0.1)
LEOPARD syndrome, n (%)	7 (0.4)	6 (0.4)	1 (0.1)
FHL1 mutations, n (%)	2 (0.1)	2 (0.1)	0 (0)
CPT II deficiency, n (%)	1 (0.1)	1 (0.1)	0 (0)

AFD= Anderson-Fabry disease, AL= immunoglobulin light chain, GSD= glycogen storage disease, HCM= hypertrophic cardiomyopathy, LEOPARD= Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, Deafness, SSA= senile systemic amyloidosis, TTR= transthyretin type.

Clinical characteristics at first evaluation

Demographic and clinical features of patients at first evaluation are described in Table 2.

Table 2. Clinical and echocardiographic features at first evaluation.

	Overall (n=1697)	**Idiopathic or sarcomeric HCM** (n=1288)	**Rare phenocopies** (n=409)	**p**
Male, n (%)	1160 (68)	860 (67)	300 (73)	0.012
Reason for diagnosis				
Incidental, n (%)	475 (29)	437 (36)	38 (10)	
Cardiac symptoms, n (%)	822 (51)	660 (54)	162 (41)	
Family screening, n (%)	180 (11)	128 (10)	52 (13)	<0.0001
One or more non cardiac symptoms, n (%)	140 (9)	0 (0)	140 (35)	
Age at diagnosis of HCM, median (IQR)	50 (38-62)	49 (37-60)	58 (44-69)	<0.0001
Age at first evaluation, median (IQR)	52 (40-63)	51 (39-61)	60 (47-69)	<0.0001
NYHA III-IV at first evaluation, n (%)	241 (14)	144 (11)	97 (24)	0.013
Rhythm at first evaluation, n (%)				
Sinus rhythm	1461 (89)	1124 (87)	337 (82)	
Atrial fibrillation/Atrial flutter	124 (8)	74 (6)	50 (12)	<0.0001
Paced	53 (3)	33 (3)	20 (5)	
Max LVWT at first evaluation, (mm), median (IQR)	18 (16-21)	18 (16-22)	16 (14-19)	<0.0001

LVED diameter at first evaluation, (mm), median (IQR)	45 (41-49)	45 (41-49)	45 (40-49)	0.145
EF at first evaluation, (%), median (IQR)	65 (57-71)	66 (60-72)	60 (48-68)	<0.0001
EF <50% at first evaluation, n (%)	145 (9)	40 (3)	105 (26)	<0.0001
LA diameter at first evaluation, (mm), median (IQR)	44 (39-49)	44 (40-49)	44 (38-48)	0.072

EF= ejection fraction, HCM= hypertrophic cardiomyopathy, IQR= interquartile range, LA= left atrium, LVED= left ventricular end diastolic, LVWT= left ventricular wall thickness, NYHA=New York Heart Association functional class.

Patients with rare phenocopies were more often diagnosed because of one or more non-cardiac symptoms [140 (35%) versus 0 (0%), p<0.0001] and were more symptomatic at first evaluation [NYHA functional class III-IV 97 (24%) versus 144 (11%), p=0.013] than patients with idiopathic HCM or HCM caused by sarcomeric protein gene mutations.

Prevalence of LV systolic impairment

Systolic impairment was present in 145 patients (9%). The prevalence of systolic impairment was higher in patients with rare phenocopies compared to patients with idiopathic or sarcomeric HCM (Table 2).

The prevalence of LV systolic dysfunction amongst patients with rare phenocopies was highest in patients with AL amyloidosis (40%, 46/115 patients) followed by SSA (38%, 18/48 patients), GSD (31%, 5/16 patients, 3 with PRKAG2 mutation), hereditary TTR amyloidosis (28%,

24/86 patients), Friedreich's ataxia (18%, 2/11 patients), mitochondrial disease (13%, 3/23 patients) and AFD (8%, 7/85 patients). None of the patients with a diagnosis of Noonan syndrome, LEOPARD syndrome, FHL1 or CPT II deficiency showed LV systolic impairment at first evaluation. In the overall population, one patient with idiopathic HCM had undergone septal myectomy and no patient had a previous alcohol septal ablation.

Age at first evaluation according to aetiology

Idiopathic or sarcomeric HCM was the most frequent diagnosis at all ages. Other disorders were distributed across all decades with a higher prevalence for syndromic and metabolic diseases in the young and cardiac amyloidosis in older age groups. Median age at first evaluation was lowest in patients with Friedreich's ataxia [20 (17-23) years), LEOPARD syndrome [23 (19-63) years], Noonan syndrome [24 (20-40) years] and GSD [24 (22-40) years] and highest in patients with hereditary TTR amyloidosis [59 (47-66) years], AL amyloidosis [63 (56-69) years] and wild-type or SSA [78 (72-81) years] (Figure 2). A similar age distribution was seen in patients with LV systolic dysfunction (Figure 3).

Prognosis in relation to aetiology and LV systolic function

Median duration of follow-up from first evaluation was 3.7 (IQR 1.6-7.2) years. In the overall population, 58 patients were assessed only at first evaluation and therefore were excluded from the outcome analysis. Two hundred and fifty (15%) patients died or underwent orthotopic heart transplantation. Death from any cause and heart transplantation were more frequent in rare phenocopies compared to idiopathic or sarcomeric HCM [129 (33%) versus 121 (10%), respectively ($p<0.0001$)] (Figure 4A). Similar results were found for heart failure-related death [34 (9%) versus

21 (2%), respectively (p<0.0001) (Figure 4B). All-cause mortality, CV death, death from heart failure and heart transplantation were all more common in patients with rare phenocopies compared to patients with idiopathic or sarcomeric HCM or non-syndromic HCM (Table 3).

Table 3. Outcomes in the overall population, idiopathic or sarcomeric HCM and in rare phenocopies.

	Overall population (1639 pts)	**Idiopathic or sarcomeric HCM** (1243 pts)	**Rare Phenocopies** (396 pts)	p
All-cause mortality/HTx n (%)	250 (15)	121 (10)	129 (33)	<0.0001
CV death/HTx, n (%)	160 (10)	89 (7)	71 (18)	<0.0001
HF death, n (%)	55 (3)	21 (2)	34 (9)	<0.0001
HTx, n (%)	33 (2)	18 (1)	15 (4)	0.006
SD, n (%)	60 (4)	41 (3)	19 (5)	<0.0001
Stroke-related death, n (%)	11 (1)	9 (1)	2 (0.5)	
Non-CV death, n (%)	46 (3)	26 (2)	20 (5)	
Unknown, n (%)	50 (3)	6 (0.5)	44 (11)	

HCM= hypertrophic cardiomyopathy, CV= cardiovascular, HF= heart failure, HTx= heart transplantation, SD= sudden death

Thirteen (9%) of the 145 patients with systolic impairment underwent heart transplantation. Kaplan Meier analysis demonstrated that all-cause mortality/heart transplantation and heart failure-related mortality were highest in patients affected by cardiac amyloidosis (Figure 5A and B). Heart failure-related deaths only occurred in patients with cardiac amyloidosis (n=21), idiopathic or sarcomeric HCM (n=21) and AFD (n=4). All-cause death/heart transplantation and death from heart failure were more frequent in patients with LV systolic dysfunction than in patients with preserved LV systolic function, ($p<0.0001$). No gender differences were present for any analyses.

DISCUSSION

To the best of our knowledge, this is the first study to assess the prevalence of LV systolic dysfunction in adult patients with HCM caused by different aetiologies. The recent ESC guidelines suggest that LV systolic impairment should be considered as diagnostic 'red flag' for less common causes of otherwise unexplained LV hypertrophy [1]. Our study confirmed this hypothesis, showing that LV systolic dysfunction is more frequent in rarer phenocopies compared to idiopathic or sarcomeric hypertrophic cardiomyopathy. Moreover, the prevalence of different phenocopies is age dependent.

Relation between aetiology and age at presentation

The starting point in this study was a clinical diagnosis of HCM based on LV wall thickness [1]. While HCM is most commonly an inherited disease caused by mutations in genes encoding sarcomeric proteins, approximately 5-10% of patients have rarer disorders which may be overlooked unless they are specifically excluded. In the most recent ESC guideline on HCM [1],

great emphasis is placed on the search for diagnostic clues or 'red flags' that point towards one of these phenocopies. This study shows that one of the most important of these diagnostic pointers is the age at presentation, as many phenocopies manifest predominantly in early, middle or late decades of life. In some instances, presentation is confined to particular age ranges; for example, wild type TTR amyloidosis in the elderly and Friedreich's ataxia in the young.

Systolic function in relation to aetiology

In most patients with idiopathic or sarcomeric HCM, LV systolic function measured using ejection fraction is within or above normal ranges due to a small LV cavity and preserved radial function, but several studies have shown that some patients develop progressive systolic impairment during follow-up. The prevalence of severe systolic impairment (arbitrarily defined as an EF of < 50%) using conventional echocardiographic criteria ranges from 2% to nearly 5%, with an annual incidence of less than 1% [3-5]. This so-called end-stage disease can develop at any age, but in the majority of patients, the time from onset of symptoms to diagnosis of severe systolic impairment is about 10-15 years [3]. The development of severe systolic heart failure is associated with a poor prognosis, with rapid progression to death or transplantation and a mortality of up to 11% per year [5].

In this study, the prevalence of severe LV systolic impairment was nine times higher in patients with rare phenocopies compared to patients with idiopathic or sarcomeric HCM. Just as with the aetiology of HCM, the clinical profile of patients with systolic impairment varied with age in that Friedreich's ataxia and GSD showed the earliest presentation with systolic impairment compared to patients with mitochondrial disease, AFD and wild-type amyloidosis in whom systolic impairment was a late event. None of the patients with a diagnosis of Noonan syndrome,

LEOPARD syndrome, FHL1 mutations or CPT II deficiency showed LV systolic impairment at first evaluation.

Impact of systolic dysfunction on prognosis

During follow-up, the rate of death and heart transplantation was three times higher in patients with rare phenocopies than in patients with idiopathic or sarcomeric HCM due to a much higher incidence of death from progressive heart failure. This finding was driven predominantly by patients with AL and TTR related amyloidosis who had the poorest survival among all the patient subgroups, a finding consistent with the known natural history of these diseases [21-23]. The overall rate of heart transplantation was low in the total study cohort, but was performed in almost 10% of patients with systolic impairment at first evaluation, highlighting the need for close monitoring of this cohort.

Clinical Implications

The term hypertrophic cardiomyopathy embraces a wide range of conditions with different natural histories and prognosis. This study shows that the presence of severe systolic impairment should prompt a systematic search for rare phenocopies informed by the age of the patient at first presentation. The implications for individual patients vary according to the underlying disease, but in some cases disease-specific therapies that impact on morbidity and prognosis are available. In patients without rare phenocopies, regular monitoring for symptomatic deterioration and progressive heart failure should be performed.

CONCLUSION

In an adult population of patient with HCM, LV systolic dysfunction is more frequent in rare causes of HCM. When combined with age at presentation it is a marker for specific aetiologies and is associated with poorer long-term survival.

Limitations

The aim of our study was not to explore the prevalence of the different diseases underlying the hypertrophic phenotype, but rather to explore the clinical relevance of LV systolic dysfunction in different HCM phenocopies.

The population in this study is heterogeneous in relation to genetic analysis (the UK population being represented by patients consecutively investigated by next generation sequencing while in the Italian population classic genetic analysis by Sanger was performed on case-by-case basis). Therefore no statistical analysis on the impact of genotype has been performed.

Data collection in the two participating centres took place over very different time periods and could have affected outcomes due to changes in treatment regimens, particularly for patients with amyloidosis.

Conflict of Interest: none declared

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Ethics approval: The National Research Ethics Service (NRES)/Ethics Committee London Harrow approval for data collection at The Heart Hospital was obtained that included waiving patient's consent given the retrospective observational nature of the work. Patients at the Department of Cardiology at the Bologna University have been approved by the appropriate local ethics committee.

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FIGURE LEGENDS

Figure 1. Patient population selection process.

This figure illustrates the selection process and number of patients in each etiological subgroup. *3 patients with Danon disease and 5 pts with AMP-protein kinase deficiency or PRKAG2.

AFD= Anderson-Fabry disease, AL= immunoglobulin light chain, CPT II= carnitine palmitoyltransferase II, EF= ejection fraction, FH= family history, FHL1= Four and a Half LIM domain protein 1, GSD= glycogen storage disease, HCM= hypertrophic cardiomyopathy, LEOPARD= Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, Deafness, SSA= senile systemic amyloidosis, TTR= transthyretin type.

Figure 2. Age at first evaluation according to main aetiologies in the overall population.

Distribution of median age at first evaluation: this was lowest in patients with Freidreich's ataxia, LEOPARD syndrome, Noonan syndrome and GSD and highest in patients with hereditary TTR amyloidosis, AL amyloidosis and wild-type or SSA. The box represents the interquartile range (IQR) and the line across the box indicates the median. The whiskers represent the highest and lowest values which are no greater than 1.5*IQR from the upper or lower edge of the box. In brackets number of patient in each group/percentage. Abbreviations as in Figure 1.

Figure 3. Age at first evaluation according to aetiology in patients with LV systolic dysfunction.

Distribution of median age at first evaluation according to aetiology in patients with LV systolic dysfunction (145 patients). Abbreviations as in Figure 1. Graph explanation as in Figure 2.

Figure 4. Outcomes in patients with idiopathic or sarcomeric HCM versus those with rare phenocopies.

Cumulative incidence of All-cause mortality or HTx (A) and HF-related death (B) in idiopathic or sarcomeric HCM versus phenocopies. Number at risk at each time point displayed on the x-axis. HCM=hypertrophic cardiomyopathy, HF=heart failure, HTx= heart transplantation.

Figure 5. Outcomes in idiopathic or sarcomeric HCM compared with specific rare phenocopies.

Cumulative incidence of All-cause mortality or HTx (A) and HF-related death (B) according to specific aetiologies. Number at risk at each time point displayed on the x-axis. Abbreviations as in Figure 4. AFD= Anderson-Fabry disease, AL= immunoglobulin light chain, HCM= hypertrophic cardiomyopathy, HF=heart failure, HTx= heart transplantation, SSA= senile systemic amyloidosis.