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Impact of Demographic Features, Lifestyle, and Comorbidities on the Clinical Expression of Hypertrophic Cardiomyopathy

Gherardo Finocchiaro, MD; Emma Magavern, MD, BA, MSc; Gianfranco Sinagra, MD; Euan Ashley, MD, PhD, MRCP; Michael Papadakis, MD, MBBS; Maite Tome-Esteban, MD, PhD; Sanjay Sharma, MD, BSc, MBChB, FRCP; Iacopo Olivotto, MD

Felix qui potuit rerum cognoscere causas

Happy is he who has been able to learn the causes of things

—Virgil, Georgiche, II, 489

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disease defined clinically by the presence of unexplained left ventricular (LV) hypertrophy (LVH). In most patients, HCM is caused by mutations in genes encoding proteins of the cardiac sarcomere.[1–4] Symptoms include dyspnea on exertion, fatigue, angina, atypical chest pain, syncope, and palpitations. A significant proportion of patients are asymptomatic throughout life and the diagnosis often follows the incidental finding of abnormal ECG results or the detection of a cardiac murmur. The natural history is variable. Many patients have a normal life expectancy, whereas others may experience disease progression with profound exercise limitation, recurrent arrhythmias, and premature death largely caused by heart failure.[5,6] Sudden cardiac death (SCD) is relatively rare, occurs more commonly in young patients, and is mainly caused by ventricular arrhythmias that can be effectively treated with an implantable cardioverter-defibrillator.[7,8]

HCM is a typical example of monogenic disease where a single nucleotide mutation is sufficient to cause a complex pathologic phenotype.[9] Genetic testing identifies pathogenic or likely pathogenic variants in 30% to 50% of patients with HCM, and over 1 000 distinct mutations in genes encoding 11 different components of the sarcomere have been identified.[10–13] Using genetic testing to identify possible mutations may help streamline family evaluation and longitudinal follow-up.[14] After 25 years of genetic testing, however, we are still unable to predict phenotypes and outcomes from a gene-based model. HCM is an extremely heterogeneous disease with regard to clinical onset and presentation, phenotype, and clinical course, even within the same pedigree. Both penetrance and expressivity are thought to be influenced by epigenetic and environmental mechanisms, although the quality and extent of these interactions remain elusive.[15]

In this review, we focus on the complex interplay between genetics and potential modifiers of disease expression including demographic features, physiological challenges such as pregnancy and physical exercise, as well as comorbid conditions. Some of the potential modifiers (Table 1) will be used as examples to discuss gene–environment interaction in this particular clinical setting.

Life Cycle

Age

Although age cannot be considered an environmental factor sensu stricto, the effects of aging on the heart are indisputable. In recent years, older patients with HCM have been increasingly recognized because of greater awareness of the disease and advances in cardiac imaging techniques. Young patients appear to have a higher risk of arrhythmic SCD, which is rare in those older than 60 years.[16] Such an inverse relationship between advanced age and SCD-related risk in HCM inevitably affects management decisions, particularly regarding implantable cardioverter-defibrillator implantation. Conversely, the burden of disease in terms of atrial fibrillation and heart failure–related complications peaks in patients aged 50 to 70 years and it may be attributable to long-standing microvascular ischemia and progressive myocardial fibrosis leading to remodeling of the left ventricle and left atrial chambers.[17] In this regard, while younger patients rarely develop heart failure-related issues, an early

From the Molecular and Clinical Sciences Research Institute Cardiology Clinical Academic Group, St George's, University of London, London, United Kingdom (G.F., M.P., M.T.-E., S.S.); Imperial College Healthcare NHS trust, St Mary's Hospital, London, United Kingdom (E.M.); Cardiovascular Department, A.O.U. Ospedali Riuniti, Trieste, Italy (G.S.); Stanford University, Palo Alto, CA (E.A.); Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy (I.O.).

Correspondence to: Iacopo Olivotto, MD, Referral Center for Cardiomyopathies, Careggi University Hospital, Largo G. Alessandro Brambilla, 3, 50134 Florence, Italy. E-mail: iacopo.olivotto@gmail.com

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Table 1. Potential Environmental Modifiers of Phenotypic Expression in HCM

Phenotypic Expression	Modifiers	Effects
LVH	Sex	↑ LVH in men
	Ethnicity	↑ LVH in Afro-Caribbean athletes
	Obesity	↑ LV mass in obese individuals
	Hypertension	↑ LVH in patients with hypertension
	Renal disease	↑ LVH in CKD
	Sport	No clear effects
	Diet	No clear effects
Microvascular dysfunction	Hypertension	↑ Microvascular ischemia
	Autoimmune disease	↑ Microvascular ischemia
	CAD	↑ Microvascular and macrovascular ischemia
	Cocaine abuse	↑ Microvascular and macrovascular ischemia
	Thrombophilic status	↑ Microvascular and macrovascular ischemia
Hemodynamic status/obstruction	Dehydration	↓ Venous return,↑ LV gradients
	Anemia	↑ LV gradients
	Thyroid disease	↑ LV gradients
	Pregnancy	↓ LV gradients
	Pharmacological treatment (inotropes, vasodilators, diuretics)	↑ LV gradients
	Acquired valvular heart disease	↑↓ LV gradients

↑ indicates increased; ↓, decreased; CAD, coronary artery disease; CKD, chronic kidney disease; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy.

onset of disease is associated with markedly increased risk of HCM complications after midlife.[17]

Pregnancy

Pregnancy is characterized by significant physiological changes in the cardiovascular system, including increases in cardiac output, extracellular fluid volume and arterial compliance, and reduction in blood pressure and total peripheral resistance. Hormonal changes include increased levels of estrogens and progesterone, which result in vasodilatation. A substantial activation of the renin-angiotensin-aldosterone system occurs early in pregnancy and results in increased plasma volume.[18] These physiological changes also affect the heart, with significant increase in LV wall thickness and mass. Preexisting cardiovascular disease can therefore be exacerbated by the adaptations that occur during gestation.[19]

Despite these concerns, pregnancy is well tolerated by asymptomatic or mildly symptomatic women with HCM. The hypertrophied LV can accommodate the rise in cardiac output and blood volume, and the reduction of systemic vascular resistance is generally without consequences on LV filling pressures. Development of heart failure symptoms is uncommon during pregnancy, occurring in <5% of patients with previously asymptomatic HCM. The most common issues are related to diastolic dysfunction, LV outflow tract (LVOT) obstruction, and arrhythmias. In pregnant patients with HCM, preexisting heart failure symptoms, pulmonary hypertension, and severe LVOT obstruction are the main predictors of maternal and neonatal events.[20] Of note, multiple pregnancies are not likely to affect the natural history of the disease, nor its phenotypic expression.[3]

Demographic Features

Ethnicity

Epidemiological data in different ethnicities show that the prevalence and clinical profile of HCM do not differ among various populations.[21] Because most of the studies addressing phenotypic expression and natural history of HCM are based on white patients, data on individuals of other ethnicities are limited. However, observations in athletes and patients with hypertension reveal that individuals of African/Afro-Caribbean descent show more significant morphological changes, degree of LVH, and ECG abnormalities compared with whites.[22] Awareness of such differences is important in order to avoid overdiagnosis of HCM in healthy individuals exhibiting phenotypes that are within physiological limits for their ethnicity. A recent study by Sheikh et al[23]

showed that black patients with HCM almost always exhibit an abnormal ECG, with high prevalence of T-wave inversion; moreover, black patients more often had apical or concentric patterns of hypertrophy compared with white patients. Although hypertension is more common in black individuals, the greater burden of LVH does not appear related to hypertension and probably rest on a polygenic basis. Indeed, the morphological differences persisted after excluding patients with hypertension and likely reflect a true impact of ethnicity on the HCM phenotype. In the same study, black patients did not exhibit a higher prevalence of conventional risk markers for SCD, and ethnicity was not a determinant of the composite primary outcome of death, cardiac arrest, or appropriate implantable cardioverter-defibrillator therapy.

Sex

The Mendelian mode of HCM inheritance is autosomal dominant, which implies that equal numbers of men and women are carriers of the underlying disease-causing mutation. However, men are consistently more prevalent in published cohorts, typically with a 3:2 ratio to women. Although male predominance may reflect a similar lack of awareness that is well recorded in other cardiovascular diseases in women, the difference in disease expression among the sexes is likely to be influenced by genetic and endocrine factors. Women with HCM are older at presentation, more symptomatic, and more likely to have resting LV obstruction compared with men.[24] While LV mass indexed for body surface area is lower in women, suggesting milder phenotypic expression[25] (Figure 1), women are more prone to heart failure–related mortality and HCM-related complications.[26,27] Furthermore, women with HCM have comparable rates of SCD compared with men,[24,28,29] although they may be less exposed to arrhythmic events triggered by strenuous exercise.[30,31] As women are less likely to be diagnosed with HCM at routine medical examination, a higher index of diagnostic suspicion and lower threshold for referral to a specialist are warranted.

Little is known regarding the impact of sex hormones on the development of myocardial hypertrophy in HCM, although the older, often postmenopausal age at presentation in women with HCM support a protective role of estrogens. Indeed, estrogens are known to have a protective role in secondary hypertrophic response, while exposure of cardiac myocytes to androgens may result in LVH. In healthy individuals, increase in cardiac mass following puberty is greater in men, and estrogens have been shown to exert preventive effects on cardiac hypertrophy.[31] However, the physiological actions of androgens in the heart remained largely unclear compared with those of estrogens. Some studies have shown that androgens are prohypertrophic,[32,33]

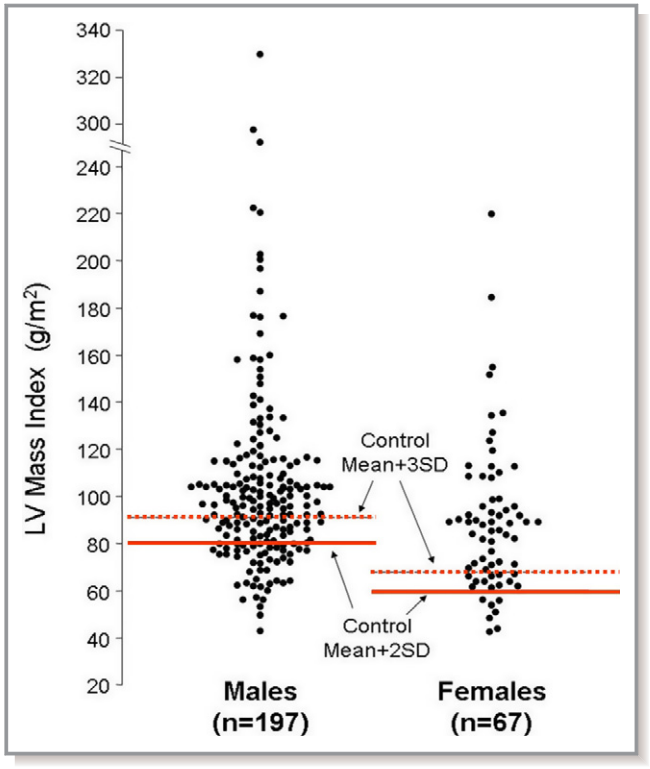

Figure 1. Sex differences in left ventricular (LV) mass in patients with hypertrophic cardiomyopathy. Men exhibit significantly higher values of indexed LV mass. Reprinted from Olivotto et al[25] with permission. Copyright ©2008, Elsevier.

via a direct androgen receptors–mediated pathway. Furthermore, a study by Lind et al[33] showed that variations at the androgen receptor gene were associated with LVH in men with HCM in a cohort of 200 unrelated patients. Experiments in mouse models carrying MYBPC3 mutations showed significant sex differences in terms of sarcomeric force generation. These differences were even more evident in mutant mice engaged in an exercise protocol, suggesting that physiological stimuli elicit a sexually dimorphic cardiac response.[32]

Habits and Lifestyle

Exercise and Sport

Regular exercise has a favorable effect on many of the established risk factors for ischemic cardiovascular disease, thereby decreasing morbidity and mortality.[33–35] However, strenuous exercise is known to trigger SCD in athletes with an underlying cardiac disease.[36,37] HCM is believed to be a common cause of SCD in young athletes,[38] and the interplay of the pathological substrate characterized by myocardial disarray, fibrosis, and microvascular remodeling with physiological mechanical stressors and potentially adverse effects of

intense exercise such as dehydration, sympathetic stimulation, electrolyte abnormalities, and acid base disturbances may trigger fatal arrhythmias during exertion.[39] Therefore, consensus statements recommend that individuals with HCM should refrain from participating in competitive physical activity.[40,41] These recommendations are based on reasonable pathophysiological assumptions and are ultimately aimed at protecting athletes by preventing SCD.

There are, however, several scientific, epidemiological, and ethical matters of debate related to exercise participation in patients with HCM. First, the rate of exercised-induced SCD in HCM is unclear. Recent data suggest that SCD occurs during sport in less than 20% of patients with a postmortem diagnosis of HCM, and that young age and male sex are the main independent variables associated with exercise-induced SCD.[42] Second, while HCM has been historically reported as the most common cause of SCD in young athletes in the United States, other conditions such as arrhythmogenic right ventricular cardiomyopathy or sudden arrhythmic death syndrome with a normal cardiac autopsy may be more frequent.[43–45] Furthermore, novel entities such as, unexplained or "idiopathic" LVH (ie, LVH without evidence of significant myocardial disarray) has been reported as a relatively common finding in athletes and nonathletes who died suddenly.[44,45] The significance of idiopathic LVH is unclear and postulated theories range from part of the spectrum of HCM, to trigger for fatal arrhythmias in individuals with an underlying arrhythmogenic syndrome, because LVH exacerbates electric instability. These data imply that the epidemiologic burden of HCM as a cause of SCD in athletes may be lower than previously reported.

Another important point of debate is whether long-term exercise has a role in the natural history of HCM. There are no data to support a detrimental effect of exercise in patients with HCM and no evidence that long-term athletic training may promote an exacerbation of the underlying disease process. In animal models, routine exercise before the development of cardiac phenotype prevented subsequent fibrosis, myocyte disarray, and induction of markers of hypertrophy in mutant myosin heavy chain mice.[46] Conversely, in non-mutant rats conditioned to run vigorously for up to 16 weeks, cardiac fibrosis, changes in ventricular function, and increased arrhythmic propensity were observed.[47] To date, none of these effects have been demonstrated in humans, and data on the effects of exercise as a natural history modifier, as seen in arrhythmogenic cardiomyopathy,[34] are lacking in HCM.

Based on the plethora of benefits of moderate exercise for the cardiovascular system and general well-being, recreational exercise should be encouraged in most individuals with HCM.[37] At present, most patients are less active than the general population and report purposefully reducing or even stopping their activity after diagnosis,[48] an attitude that is likely to adversely affect their long-term outcome. A recent randomized study showed that moderate-intensity exercise, compared with usual activity, resulted in a significant increase in exercise participation and capacity in patients with HCM, without a significant increase in the burden of arrhythmias or other adverse events.[49] This study supports regular adoption of aerobic training in HCM following the Greek philosophical principle of *Metron ariston* (ie, moderation is best), based on the tailoring of exercise activity to reasonable thresholds based on age and fitness level.

Another important matter of debate is the management of genotype positive–phenotype negative (G+/P−) individuals, a rapidly increasing population following the widespread adoption of genetic testing. Often, individuals identified by this term have no evidence of LVH but are not truly "phenotype negative," because of the presence of ancillary HCM manifestations such as LV crypts, mitral valve abnormalities, and mild regional diastolic impairment at the septal level. Although the European Society of Cardiology recommendation is restrictive and states that athletes with a G+/P− should have the same limitations as patients with overt HCM, a detrimental role of exercise in these individuals has not been demonstrated,[50] and their access to competitive sports is not restricted in the United States.

Diet and Fluid Intake

The role of dietary habits is crucial to both the development and prevention of cardiovascular disease. Diet and lifestyle have been a main focus of research in coronary artery disease (CAD) for decades.[51] Benefits and harms of diet are not limited to the mechanistic interactions underlying the progression of atherosclerosis but extend to other scenarios, including primary cardiomyopathies. For example, a soy diet was associated with progressive to severe end-stage cardiomyopathy and heart failure in a transgenic mouse model of α-myosin heavy chain HCM, possibly through induction of augmented cell growth and apoptosis. Conversely, such evolution was prevented by a casein diet.[52] To date, however, the impact of different dietary regimens on patients with HCM has not been investigated.

In clinical practice, apart from the obvious implications related to weight control and cardiovascular prevention, dietary advice to patients with HCM should deal with the effects of meals on quality of life and symptomatic status. Following food intake, splanchnic blood flow sequestration results in decreased circulating plasma volume, thereby increasing LV outflow gradients.[53,54] Thus, postprandial symptoms of angina, dyspnea and—occasionally—syncope, are common in obstructive HCM. Patients should be recommended to avoid large meals and reduce levels of

postprandial activity. Dehydration, which results in reduced preload, increased contractility, and possibly a worsening of dynamic LV obstruction should also be avoided. Finally, alcohol should be consumed with moderation by patients with HCM, as it has been shown to decrease arterial blood pressure and increase systolic anterior motion severity and degree of intraventricular obstruction[55] (Figure 2).

Acquired Comorbidities

Hypertension

Hypertension is conventionally regarded as a potential exclusion criterion for the diagnosis of HCM.[3] However, many patients with unequivocal HCM may present with or develop some degree of hypertension, given the high prevalence of hypertension in the adult population.[56] In most patients with hypertension, LV wall thickness is normal or only mildly increased (≤13 mm). Only a minority of patients, often with secondary forms of hypertension or of Afro-Caribbean or African descent, have more substantial hypertrophy (up to 16 mm) and fall into a "grey zone" of potential overlap with HCM.[23] When differentiating hypertensive heart disease from HCM, a number of additional features, including mitral valve abnormalities and lack of extracardiac organ damage may be suggestive of the latter.[57]

In a recent study, hypertension was an independent predictor of outcome in patients with HCM, irrespective of ethnicity, sex, or age.[23] A significant increase in afterload and neuroendocrine activation may further increase LV mass and adversely affect the clinical expression of the disease. Aggressive management of uncontrolled hypertension is

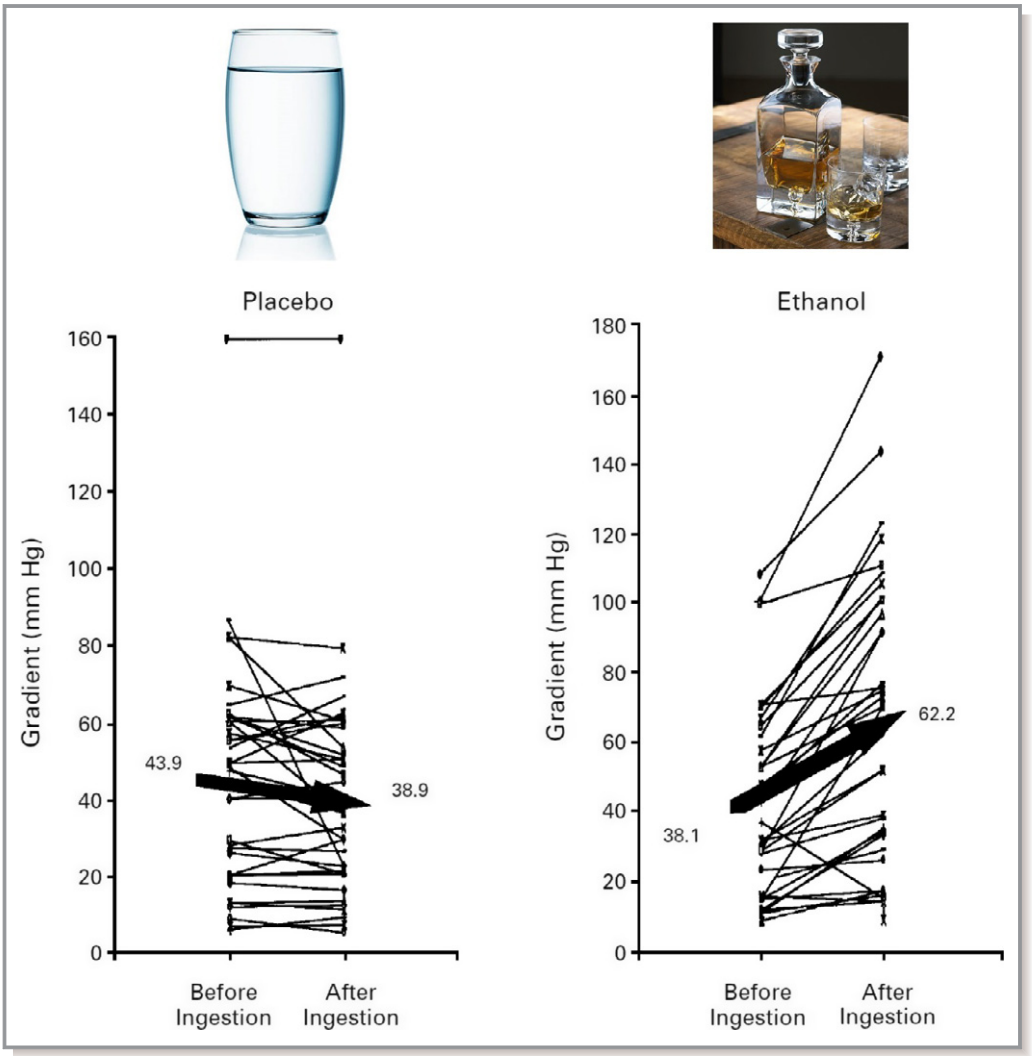

Figure 2. Alcohol and left ventricular (LV) obstruction in hypertrophic cardiomyopathy. After ethanol ingestion the average LV gradients increase from an average of 38.1 to 62.2 mm Hg. Reprinted from Paz et al[55] with permission. Copyright ©1996, the Massachusetts Medical Society.

therefore mandatory in HCM, but may be challenging, as most vasodilators will exacerbate dynamic LVOT obstruction.[58,59]

The question of whether a quota of secondary LVH might worsen the phenotypic expression of HCM in patients with hypertension remains unresolved. Afterload increase and neuroendocrine activation may plausibly contribute to an augmented LV mass. Likewise, appropriate treatment of hypertension might reduce "nongenetic" LVH. This intuitive concept, although not proven, is supported by studies showing regression of LVH following septal reduction therapies. Of note, reduction of LV mass following resolution of afterload mismatch occurred in regions of HCM hearts remote from the septum, suggesting that reverse remodeling may occur in this disease on removal of pathologic environmental stimuli.[60,61] This general concept of partial reversibility of LVH in patients with HCM requires further investigation and is of relevance to other potential determinants such as sport, obesity, and renal failure.

Another interesting concept is that polymorphisms in the renin-angiotensin-aldosterone system, which have been associated with LVH in untreated hypertension, may be potential disease modifiers in HCM.[62] and may specifically impact the clinical phenotype of HCM.[63]

Obesity

Obesity is a rising public health problem and a known risk factor for cardiovascular diseases. Because of its maladaptive effects on various cardiovascular risk factors and its adverse effects on cardiac structure and function, obesity has a major impact on morbidity and mortality. As recently demonstrated, its prevalence in HCM is remarkably high, reaching almost 40%. Obesity is independently associated with increased LV mass (Figure 3), an adverse prognostic factor in HCM, contributing to more rapid clinical progression and worsening of heart failure symptoms.[64] Interestingly, however, LV mass increase in obese patients with HCM seems to merely reflect LV cavity enlargement, physiologically aimed at increasing cardiac output[65] to meet the increased requirements of excessive body weight. Conversely, maximal LV thickness is similar in normal weight versus obese patients with HCM, suggesting that the genetic design of asymmetric septal LVH is independent of body mass index.[48] Of note, LV obstruction is more common in obese patients and observed in more than 50% with body mass index >30, because of distinctively higher predisposition to provocable (as opposed to resting) gradients. A beneficial impact of weight reduction on the severity of LVOT obstruction is plausible but remains unproven.[66] Finally, although the role of obesity as an independent risk factors for SCD in HCM has not been established, the susceptibility of obese patients with HCM to fatal arrhythmias is a potential area of research.[67]

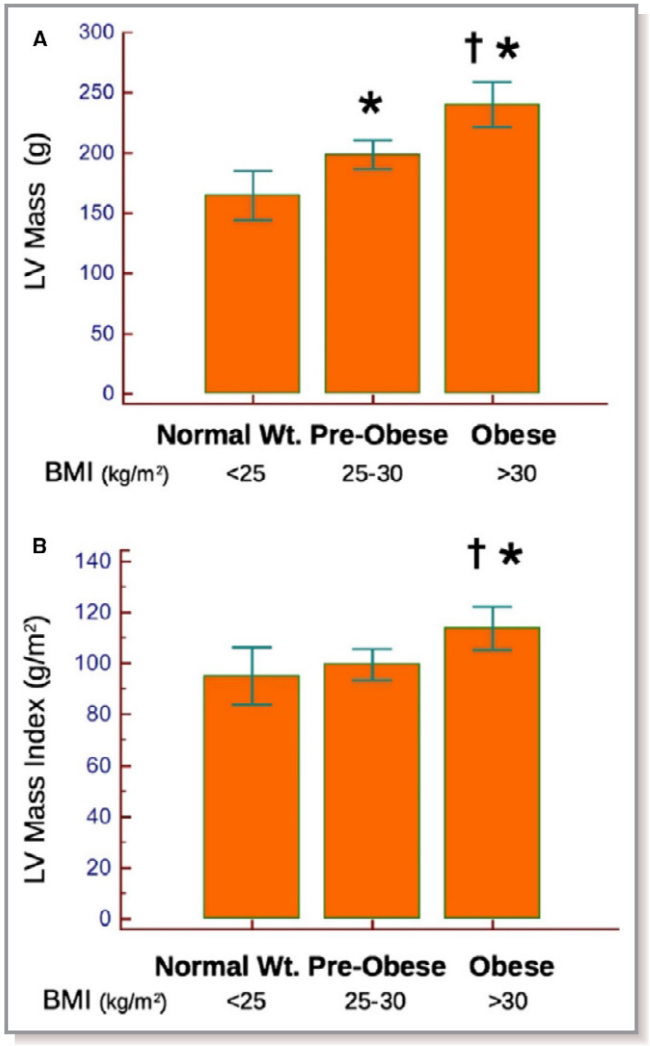

Figure 3. Relationship between left ventricular (LV) mass and body mass index (BMI) (A) and LV mass indexed for body surface area and BMI (B) in patients with hypertrophic cardiomyopathy. Obese individuals (BMI >30) exhibit higher values of LV mass and indexed LV mass. Reprinted from Olivotto et al[64] with permission. Copyright ©2013, Elsevier.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common condition in Western countries, characterized by repetitive interruption of ventilation and hypoxia during sleep, which affects a large proportion of patients with hypertension, obesity, CAD, atrial fibrillation, and stroke. In peripheral OSA this is caused by collapse of the pharyngeal airway, while central OSA is related to malfunction of the respiratory control centers in the brainstem.

In recent years there have been rapid advances in the understanding of the relationship between OSA and cardiovascular disease, including HCM.[68] OSA has been reported in up to 70% of patients with HCM.[69] LVOT obstruction is

generally exacerbated by sympathetic stimulation, and the nocturnal hypoxia-induced hyperadrenergic state characteristic of OSA would be expected to worsen the hemodynamics of HCM. This vicious pathophysiological cycle translates into increased symptom burden during the day. Furthermore, peripheral vasoconstriction, apnea-induced hypoxemia, carbon dioxide retention, renal retention of salt and water, and increased renin-angiotensin-aldosterone activity may contribute to arrhythmogenesis in an already vulnerable pathological substrate.[70] Whether OSA is associated with a higher rate of ventricular arrhythmias or SCD and in general with adverse prognosis in HCM remains unclear. Nevertheless, treatment of sleep apnea, whether by weight loss, continuous positive airway pressure, or postural therapy provides important benefit in the general population and should be sought in patients with HCM.

Coronary Artery Disease

Myocardial ischemia is often observed in patients with HCM, occurring at the microvascular level as a result of structural abnormalities of the intramural coronary arterioles, characterized by thickening of the intima and medial layers of the vessel wall associated with decreased luminal cross-sectional area.[71,72] Adult patients with HCM are not immune from epicardial CAD, which may be difficult to diagnose, given the high frequency of microvascular angina and the striking ECG repolarization abnormalities present at rest, which hinder the interpretation of exercise ECG testing. Concomitant atherosclerotic disease has an important impact on the natural course of HCM. Given the increased myocardial mass and high myocardial oxygen demand, patients with HCM are particularly susceptible to the additional ischemic burden of one or multiple epicardial coronary artery stenosis.[73] Not unexpectedly, CAD is a major prognostic indicator in HCM and is associated with an increase in overall mortality, SCD, and cardiac events, with a synergistic rather than additive effect.[56] Preventive strategies for atherosclerotic disease should always be considered in patients with HCM and the standards for control of modifiable cardiovascular risk factors should arguably reflect those used for secondary rather than primary prevention of CAD because of the intrinsic frailty of the HCM myocardium to ischemic insults.

Myocardial bridging is a rare but modifiable mechanism of ischemia, acute myocardial infarction, and even SCD in young patients with HCM.[74] Myocardial bridging occurs when the epicardial coronary arteries, usually the proximal left anterior descending artery, are intramyocardial, resulting in systolic compression of a coronary artery on coronary angiography. While bridging also occurs in normal healthy controls, it is much more common in patients with HCM, reaching a prevalence of 30% to 40%. Because only a fraction of these lesions have been associated with SCD, generally in children, the role of bridging as a risk predictor in adult patients is debated but probably limited. Only when associated with clear hemodynamic abnormalities and symptoms, myocardial bridging should be treated with a surgical deroofing procedure.[75]

Sarcomere Protein Gene Profile and Predisposition to Cardiac Disease

Sarcomere gene mutations have been identified in the general population by large-scale screening studies. Most carriers do not have a cardiomyopathy and may express no or only mild and nonspecific phenotypic stigmata. However, these variants seem to retain a generic capacity to trigger cardiac disease in the presence of environmental stimuli, creating a sort of nonspecific frailty of the myocardium. In a landmark study, a common 25 mb MYBPC3 deletion was associated with increased risk of heart failure in South Asians exposed to secondary risk factors, such as hypertension and hypercholesterolemia, posing a lifelong threat to carriers.[76] Furthermore, a role for truncating titin mutations has been recently proposed in the development of peripartum cardiomyopathy,[77] suggesting the possible interaction between a genetic predisposition and additional environmental (pregnancy) or genetic stimuli. These observations add a broader dimension to the interactions between cardiomyopathies and the environment: from relatively uncommon, genetically driven diseases that are only modestly influenced by external stimuli, to a common genetic trait that is not pathogenic per se, but may provide predisposition to cardiac disease in the presence of risk factors and high-risk lifestyles (Figure 4). Understanding these complex interactions may prove critical to the identification of novel therapeutic targets for cardiovascular disease in the future.

Conclusions

Our genetic destiny is hardly written in stone. Virtually all human diseases result from the interaction of genetic susceptibility factors with modifiable environmental influences. When we observe that even “classic” inherited diseases can be modified by environmental conditions, it becomes clear that the relationship between the two is much more complex than a simple one gene–one disease model linear relationship. HCM is not an exception to this general rule. Overall, however, physiological stimuli and comorbidities seem to exert a modest impact especially on the phenotypic expression of HCM. Future research targeting HCM variability should rather focus on molecular aspects including modifier genes, epigenetic factors, and the role of regulatory systems

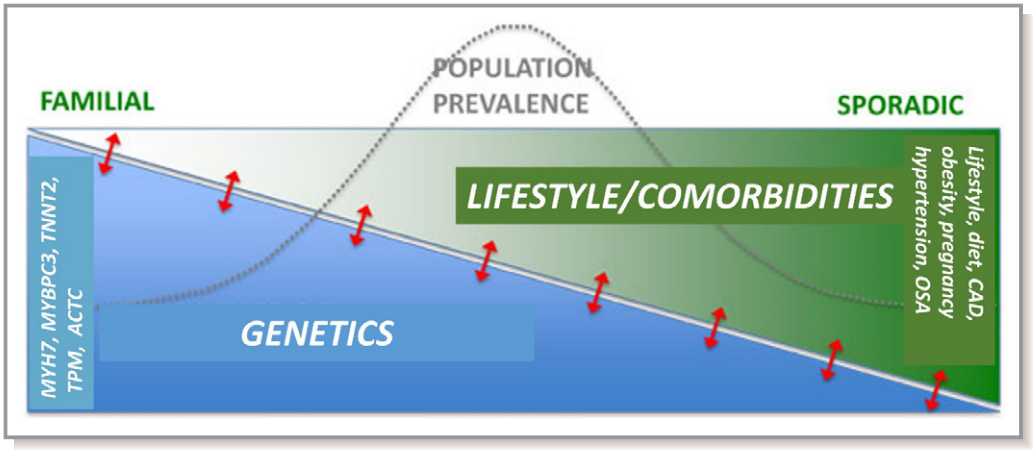

Figure 4. Continuum between genetic predisposition and environmental influences in hypertrophic cardiomyopathy. Multiple variants usually have a severe phenotypic expression that is less likely to be dependent from environment, while, in individuals harboring a single mutation, the effect of other acquired conditions may be more relevant. Multiple variants, each with small effect size, may interact with nongenetic factors to produce a hypertrophic cardiomyopathy phenotype. Genetic variants recognized as pathogenic may be present in healthy individuals where the phenotypic expression emerges only after the interaction with a specific environmental factor. CAD indicates coronary artery disease; OSA, obstructive sleep apnea.

such as microRNAs, the ubiquitine-proteasome complex, or nonsense-mediated RNA decay.[78,79]

Nevertheless, identifying modifiable risk factors that may aggravate HCM phenotype and the clinical course remains important in clinical practice, even in the absence of specific studies, along the general principles of contemporary cardiovascular medicine. Because of the intrinsic fragility of HCM hearts, it may be reasonable to manage patients according to the standards of established atherosclerotic disease, ie, of secondary rather than primary cardiovascular prevention, including strict targets for lipid profile, blood pressure and weight control, and lifestyle advice including appropriate exercise and diet (Table 2).

In the era of evidence-based medicine, the conundrum behind gene-environment interactions in genetic inherited cardiac diseases should be unraveled through improved access to empiric knowledge from randomized control trials, as well as, increasingly, from "Big Data."[80] Extensive research is warranted to identify environmental factors that may effectively act as natural history modifiers. Only through a deepened understanding of this interplay we will be able to address the many questions related to the extreme heterogeneity of clinical expression and natural history of HCM.

Table 2. Proposed Management of Modifiable Risk Factors in Patients With HCM

Lifestyle/Clinical Variables	Possible Effects
LDL <100 mg/dL*	↓ Risk of CAD and myocardial ischemia
BP <130/80 mm Hg*	↓ Risk of secondary LVH caused by increased afterload
Moderate exercise	Improvement in diastolic function and exercise capacity ↓ Risk of obesity
Weight management	↓ Risk of obesity ↓ Risk of development of a more marked LVH caused by increased afterload

↓ indicates decreased; BP, blood pressure; HCM, hypertrophic cardiomyopathy; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy.
*The standards for control of modifiable cardiovascular risk factors should arguably recapitulate those used for secondary prevention in patients with coronary artery disease (CAD), in all genetic cardiomyopathies, based on the principle that superimposed atherosclerotic disease seems to have synergistic rather than additive effects.

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Disclosures

None.

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Impact of Demographic Features, Lifestyle, and Comorbidities on the Clinical Expression of Hypertrophic Cardiomyopathy

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