

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

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*Felix qui potuit rerum cognoscere causas*

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

—Virgil, *Georgics*, II, 489

**H**ypertrophic 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.<sup>1–4</sup> 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.<sup>5,6</sup> 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.<sup>7,8</sup>

HCM is a typical example of monogenic disease where a single nucleotide mutation is sufficient to cause a complex pathologic phenotype.<sup>9</sup> 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.<sup>10–13</sup> Using genetic testing to identify possible mutations may help streamline family evaluation and longitudinal follow-up.<sup>14</sup> 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.<sup>15</sup>

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.<sup>16</sup> 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.<sup>17</sup> In this regard, while younger patients rarely develop heart failure-related issues, an early

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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.<sup>17</sup>

## 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.<sup>18</sup> 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.<sup>19</sup>

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.<sup>20</sup> Of note, multiple pregnancies are not likely to affect the natural history of the disease, nor its phenotypic expression.<sup>3</sup>

## Demographic Features

### Ethnicity

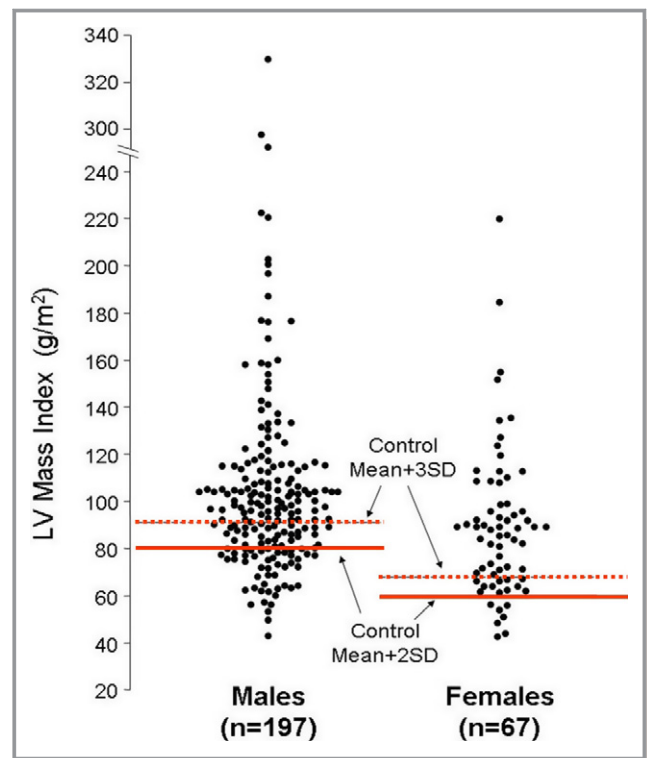
Epidemiological data in different ethnicities show that the prevalence and clinical profile of HCM do not differ among various populations.<sup>21</sup> Because most of the studies addressing phenotypic expression and natural history of HCM are based on white patients, data on individuals of other ethnicities 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.<sup>22</sup> 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<sup>23</sup>

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.<sup>24</sup> While LV mass indexed for body surface area is lower in women, suggesting milder phenotypic expression<sup>25</sup> (Figure 1), women are more prone to heart failure-related mortality and HCM-related complications.<sup>26,27</sup> Furthermore, women with HCM have comparable rates of SCD compared with men,<sup>24,28,29</sup> although they may be less exposed to arrhythmic events triggered by strenuous exercise.<sup>30,31</sup> 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.<sup>31</sup> 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,<sup>32,33</sup>



**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 Olivetto et al<sup>25</sup> with permission. Copyright ©2008, Elsevier.

via a direct androgen receptors-mediated pathway. Furthermore, a study by Lind et al<sup>33</sup> 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.<sup>32</sup>

## 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.<sup>33–35</sup> However, strenuous exercise is known to trigger SCD in athletes with an underlying cardiac disease.<sup>36,37</sup> HCM is believed to be a common cause of SCD in young athletes,<sup>38</sup> 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.<sup>39</sup> Therefore, consensus statements recommend that individuals with HCM should refrain from participating in competitive physical activity.<sup>40,41</sup> 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.<sup>42</sup> 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.<sup>43–45</sup> 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.<sup>44,45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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,<sup>34</sup> 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.<sup>37</sup> At present, most patients are less active than the general population and report purposefully reducing or even

stopping their activity after diagnosis,<sup>48</sup> 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.<sup>49</sup> 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,<sup>50</sup> 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.<sup>51</sup> 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  $\alpha$ -myosin heavy chain HCM, possibly through induction of augmented cell growth and apoptosis. Conversely, such evolution was prevented by a casein diet.<sup>52</sup> 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.<sup>53,54</sup> 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<sup>55</sup> (Figure 2).

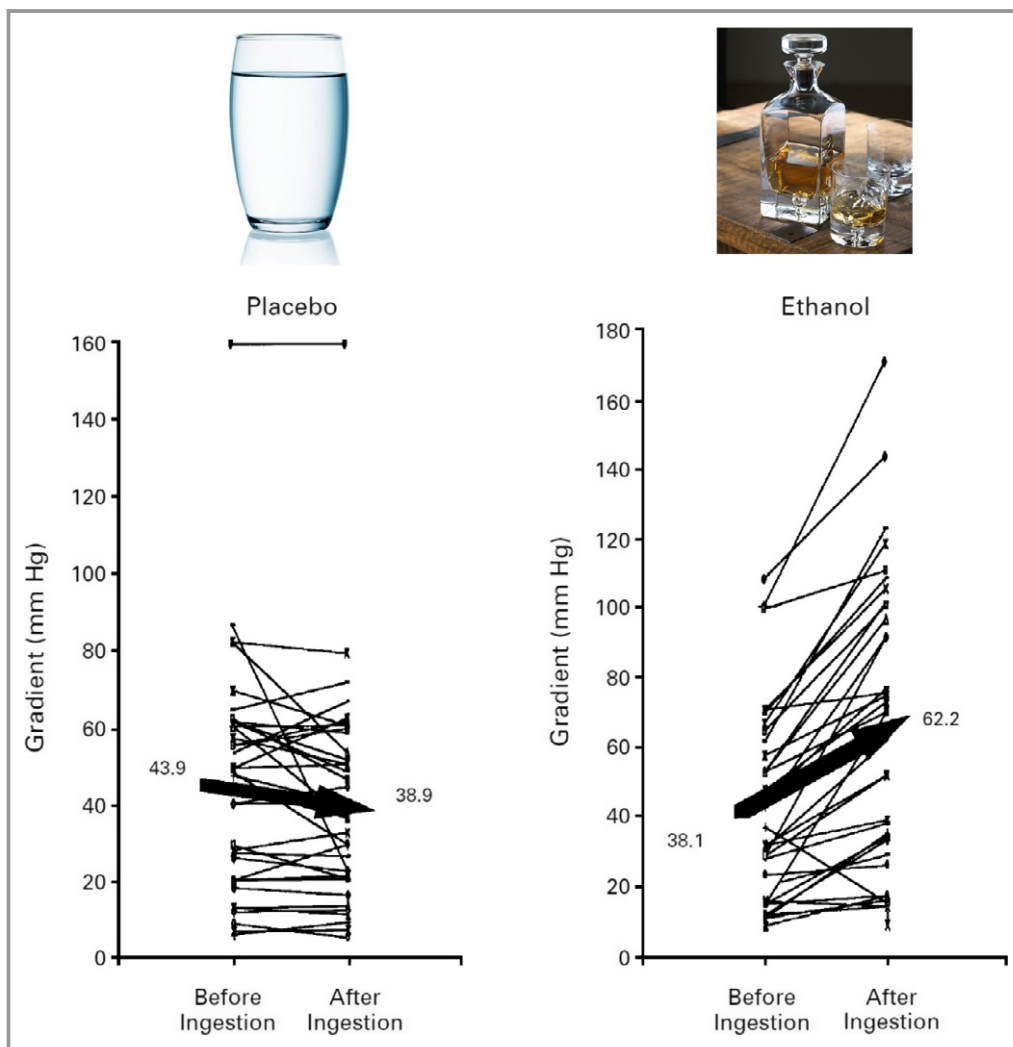
## Acquired Comorbidities

### Hypertension

Hypertension is conventionally regarded as a potential exclusion criterion for the diagnosis of HCM.<sup>3</sup> 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.<sup>56</sup> In most patients with hypertension, LV wall thickness is normal or only mildly increased ( $\leq 13$  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.<sup>23</sup> 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.<sup>57</sup>

In a recent study, hypertension was an independent predictor of outcome in patients with HCM, irrespective of ethnicity, sex, or age.<sup>23</sup> 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<sup>55</sup> with permission. Copyright ©1996, the Massachusetts Medical Society.

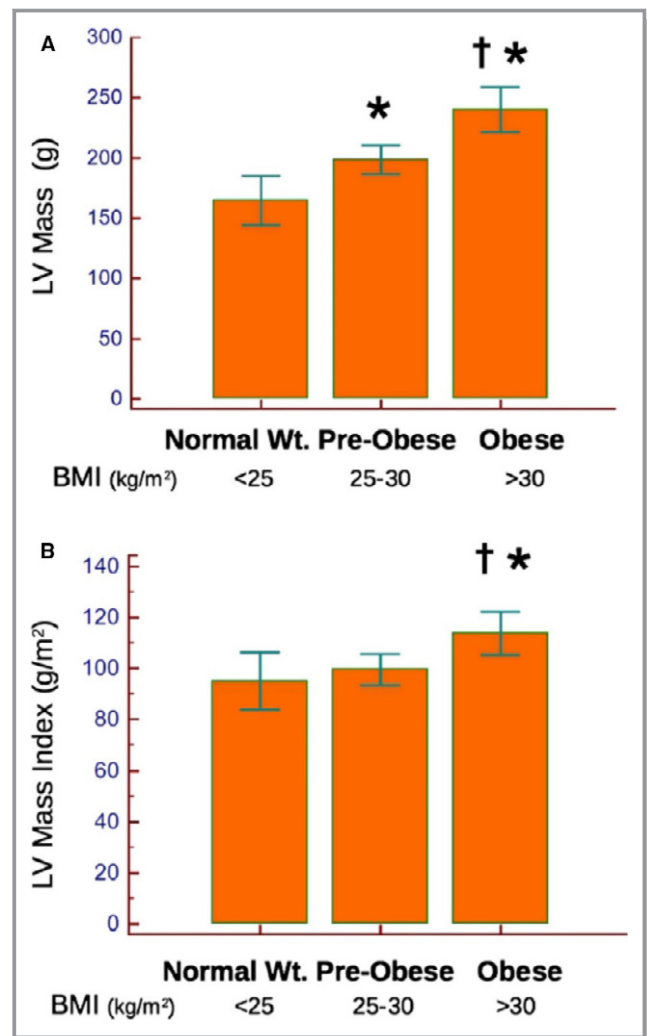
therefore mandatory in HCM, but may be challenging, as most vasodilators will exacerbate dynamic LVOT obstruction.<sup>58,59</sup>

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.<sup>60,61</sup> 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.<sup>62</sup> and may specifically impact the clinical phenotype of HCM.<sup>63</sup>

## 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.<sup>64</sup> Interestingly, however, LV mass increase in obese patients with HCM seems to merely reflect LV cavity enlargement, physiologically aimed at increasing cardiac output<sup>65</sup> 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.<sup>48</sup> 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 provokable (as opposed to resting) gradients. A beneficial impact of weight reduction on the severity of LVOT obstruction is plausible but remains unproven.<sup>66</sup> 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.<sup>67</sup>



**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 Olivetto et al<sup>64</sup> 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.<sup>68</sup> OSA has been reported in up to 70% of patients with HCM.<sup>69</sup> 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.<sup>70</sup> 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.<sup>71,72</sup> 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.<sup>73</sup> 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.<sup>56</sup> 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.<sup>74</sup> 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

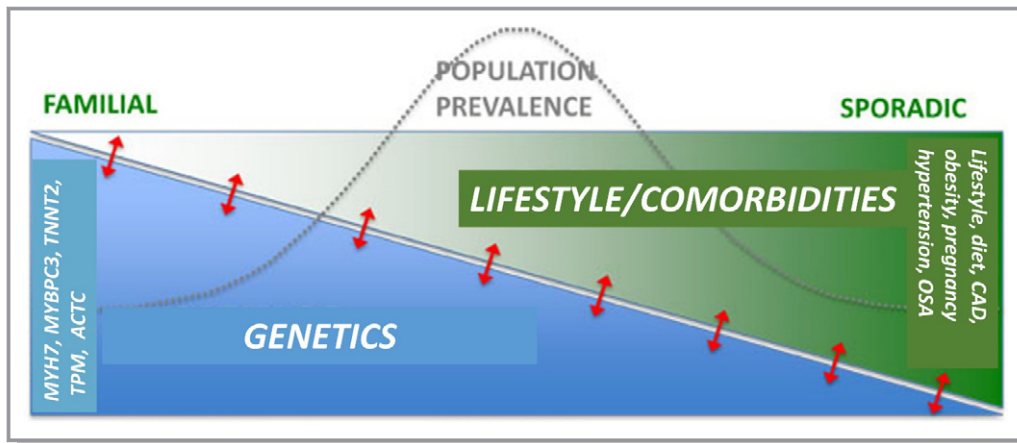
of these lesions have been associated with SCD, generally in children, the role of bridging as a risk predictor in adult patients is debated but probably limited. Only when associated with clear hemodynamic abnormalities and symptoms, myocardial bridging should be treated with a surgical deroofing procedure.<sup>75</sup>

### 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.<sup>76</sup> Furthermore, a role for truncating titin mutations has been recently proposed in the development of peripartum cardiomyopathy,<sup>77</sup> 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 ubiquitin-proteasome complex, or nonsense-mediated RNA decay.<sup>78,79</sup>

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.”<sup>80</sup> 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.

## References

- Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet*. 2013;381:242–255.
- Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I, Biller L, Lesser JR, Udelson JE, Manning WJ, Appelbaum E. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2009;54:220–228.
- Authors/Task Force Members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.
- Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e783–e831.
- Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart*. 2006;92:785–791.
- Maron BJ, Braunwald E. Evolution of hypertrophic cardiomyopathy to a contemporary treatable disease. *Circulation*. 2012;126:1640–1644.
- Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. *Circulation*. 2010;121:445–456.
- O'Mahony C, Elliott P, McKenna W. Sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2013;6:443–451.
- Ho CY. Genetics and clinical destiny: improving care in hypertrophic cardiomyopathy. *Circulation*. 2010;122:2430–2440.
- Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2014;89:727–737.
- Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, Shen J, McLaughlin HM, Clark EH, Babb LJ, Cox SW, DePalma SR, Ho CY, Seidman JG, Seidman CE, Rehm HL. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. *Genet Med*. 2015;17:880–888.
- Murphy SL, Anderson JH, Kapplinger JD, Kruisselbrink TM, Gersh BJ, Ommen SR, Ackerman MJ, Bos JM. Evaluation of the Mayo Clinic phenotype-based genotype predictor score in patients with clinically diagnosed hypertrophic cardiomyopathy. *J Cardiovasc Transl Res*. 2016;9:153–161.
- Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. *J Am Coll Cardiol*. 2010;55:1444–1453.
- Wang L, Seidman JG, Seidman CE. Narrative review: harnessing molecular genetics for the diagnosis and management of hypertrophic cardiomyopathy. *Ann Intern Med*. 2010;152:513–520, W181.
- Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ Heart Fail*. 2012;5:535–546.
- Maron BJ, Rowin EJ, Casey SA, Haas TS, Chan RHM, Udelson JE, Garberich RF, Lesser JR, Appelbaum E, Manning WJ, Maron MS. Risk stratification and outcome of patients with hypertrophic cardiomyopathy  $\geq 60$  years of age. *Circulation*. 2013;127:585–593.
- Ho CY, Day SM, Ashley EA, Michels M, da Costa Pereira A, Fox J, Caletshu CA, Cirino AL, Colan SD, Wroldstad D, Green E, Olivotto I. Evidence-based examination of prevailing genotype-phenotype correlations in hypertrophic cardiomyopathy: findings from a Multicenter International Collaboration. In: AHA 2016.
- Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation*. 2014;130:1003–1008.
- Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part I. *J Am Coll Cardiol*. 2016;68:396–410.
- Autore C, Conte MR, Piccinino M, Bernabò P, Bonfiglio G, Bruzzi P, Spirito P. Risk associated with pregnancy in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1864–1869.
- Maron BJ. Hypertrophic cardiomyopathy: an important global disease. *Am J Med*. 2004;116:63–65.
- Sheikh N, Papadakis M, Ghani S, Zaidi A, Gati S, Adami PE, Carre F, Schnell F, Wilson M, Avila P, McKenna W, Sharma S, Carré F, Schnell F, Wilson M, Avila P, McKenna W, Sharma S. Comparison of electrocardiographic criteria for the detection of cardiac abnormalities in elite black and white athletes. *Circulation*. 2014;129:1637–1649.
- Sheikh N, Papadakis M, Panoulas VF, Prakash K, Millar L, Adami P, Zaidi A, Gati S, Wilson M, Carr-White G, Tomé MTE, Behr ER, Sharma S. Comparison of hypertrophic cardiomyopathy in Afro-Caribbean versus white patients in the UK. *Heart*. 2016;102:1797–1804.
- Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, Udelson JE, Cecchi F, Maron BJ. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:480–487.
- Olivotto I, Maron MS, Autore C, Lesser JR, Rega L, Casolo G, De Santis M, Quarta G, Nistri S, Cecchi F, Salton CJ, Udelson JE, Manning WJ, Maron BJ. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2008;52:559–566.
- Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc*. 2014;3:e001002. DOI: 10.1161/JAHA.114.001002.
- Nijenkamp LL, Güçlü A, Appelman Y, van der Velden J, Kuster DW. Sex-dependent pathophysiological mechanisms in hypertrophic cardiomyopathy: implications for rhythm disorders. *Heart Rhythm*. 2015;12:433–439.
- Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NAM, Favale S, Piccinino M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298:405–412.
- Maron BJ, Haas TS, Duncanson ER, Garberich RF, Baker AM, Mackey-Bojack S. Comparison of the frequency of sudden cardiovascular deaths in young competitive athletes versus nonathletes: should we really screen only athletes? *Am J Cardiol*. 2016;117:1339–1341.
- Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and epidemiology of sudden deaths in young competitive athletes: from the United States National Registry. *Am J Med*. 2016;129:1170–1177.
- Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. *J Am Coll Cardiol*. 2013;61:1027–1040.
- Najafi A, Schlossarek S, van Deel ED, van den Heuvel N, Güçlü A, Goebel M, Kuster DW, Carrier L, van der Velden J. Sexual dimorphic response to exercise in hypertrophic cardiomyopathy-associated MYBPC3-targeted knock-in mice. *Pflugers Arch*. 2015;467:1303–1317.
- Lind JM, Chiu C, Ingles J, Yeates L, Humphries SE, Heather AK, Semsarian C. Sex hormone receptor gene variation associated with phenotype in male hypertrophic cardiomyopathy patients. *J Mol Cell Cardiol*. 2008;45:217–222.
- Shah RV, Murthy VL, Colangelo LA, Reis J, Venkatesh BA, Sharma R, Abbasi SA, Goff DC, Carr JJ, Rana JS, Terry JG, Bouchard C, Sarzynski MA, Eisman A, Neilan T, Das S, Jerosch-Herold M, Lewis CE, Carnethon M, Lewis GD, Lima JAC. Association of fitness in young adulthood with survival and cardiovascular risk: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA Intern Med*. 2016;176:87–95.
- Sharma S, Merghani A, Mont L. Exercise and the heart: the good, the bad, and the ugly. *Eur Heart J*. 2015;36:1445–1453.
- D'Silva A, Sharma S. Management of young competitive athletes with cardiovascular conditions. *Heart*. 2017;103:463–473.
- Finocchiaro G, Sharma S. The safety of exercise in individuals with cardiomyopathy. *Can J Cardiol*. 2016;32:467–474.
- Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA*. 1996;276:199–204.
- Sharma S, Merghani A, Gati S. Cardiac screening of young athletes prior to participation in sports: difficulties in detecting the fatally flawed among the fabulously fit. *JAMA Intern Med*. 2015;175:125–127.
- Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NAM, Cooper LT, Link MS, Maron MS, Levine BD, Sica D, Ferdinand K, White WB, Zipes DP, Kovacs RJ, Maron BJ, Link MS, Ackerman MJ, Kovacs RJ, Myerburg RJ, Shafer KM, Warnes CA, Washington RL, Levine BD, Washington RL, Baggish

- AL, Kovacs RJ, Maron MS, Zipes DP, Kovacs RJ, Maron BJ, Link MS, Maron MS, Harris KM, Kovacs RJ, Maron BJ, Myerburg RJ, Shafer KM, Warnes CA, Washington RL, Sica D, Ferdinand K, White WB, Maron BJ, Levine BD, Washington RL, Baggish AL, Kovacs RJ, Maron MS. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis. *J Am Coll Cardiol*. 2015;66:2362–2371.
41. Mont L, Pelliccia A, Sharma S, Biffi A, Borjesson M, Brugada Terradellas J, Carré F, Guasch E, Heidbuchel H, La Gerche A, Lampert R, McKenna W, Papadakis M, Priori SG, Scanavacca M, Thompson P, Sticherling C, Viskin S, Wilson M, Corrado D; Reviewers, Lip GY, Gorenek B, Blomström Lundqvist C, Merkely B, Hindricks G, Hernández-Madrid A, Lane D, Boriani G, Narasimhan C, Marquez MF, Haines D, Mackall J, Manuel Marques-Vidal P, Corra U, Halle M, Tiberi M, Niebauer J, Piepoli M. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAEC. *Eur J Prev Cardiol*. 2017;24:41–69.
  42. Finocchiaro G, Papadakis M, Sharma S, Sheppard M. Sudden cardiac death. *Eur Heart J*. 2017;38:1280–1282.
  43. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol*. 2003;42:1959–1963.
  44. Finocchiaro G, Papadakis M, Robertus J-L, Dhutia H, Steriotis AK, Tome M, Mellor G, Merghani A, Malhotra A, Behr E, Sharma S, Sheppard MN. Etiology of sudden death in sports insights from a United Kingdom regional registry. *J Am Coll Cardiol*. 2016;67:2108–2115.
  45. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, Drezner JA. Incidence, cause, and comparative frequency of sudden cardiac death in national collegiate athletic association athletes: a decade in review. *Circulation*. 2015;132:10–19.
  46. Konhilas JP, Watson PA, Maass A, Boucek DM, Horn T, Stauffer BL, Luckey SW, Rosenberg P, Leinwand LA. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res*. 2006;98:540–548.
  47. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation*. 2011;123:13–22.
  48. Reineck E, Rolston B, Bragg-Gresham JL, Salberg L, Baty L, Kumar S, Wheeler MT, Ashley E, Saberi S, Day SM. Physical activity and other health behaviors in adults with hypertrophic cardiomyopathy. *Am J Cardiol*. 2013;111:1034–1039.
  49. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, Concannon M, Dries AM, Shmargad Y, Salisbury H, Kumar S, Herrera JJ, Myers J, Helms AS, Ashley EA, Day SM. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. *JAMA*. 2017;317:1349–1357.
  50. Pelliccia A, Fagard R, Bjørnstad HH, Anastassakis A, Arbustini E, Assanelli D, Biffi A, Borjesson M, Carré F, Corrado D, Delise P, Dorwarth U, Hirth A, Heidbuchel H, Hoffmann E, Mellwig KP, Panhuyzen-Goedkoop N, Pisani A, Solberg EE, van-Buuren F, Vanhees L, Blomstrom-Lundqvist C, Deligiannis A, Dugmore D, Glikson M, Hoff PI, Hoffmann A, Hoffmann E, Horstkotte D, Nordrehaug JE, Oudhof J, McKenna WJ, Penco M, Priori S, Reybrouck T, Senden J, Spataro A, Thiene G; Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology, Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2005;26:1422–1445.
  51. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving postprandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol*. 2008;51:249–255.
  52. Stauffer BL, Konhilas JP, Luczak ED, Leinwand LA. Soy diet worsens heart disease in mice. *J Clin Invest*. 2006;116:209–216.
  53. Gilligan DM, Marsonis A, Joshi J, Nihoyannopoulos P, Ghatel MA, Bloom SR, Oakley CM. Cardiovascular and hormonal responses to a meal in hypertrophic cardiomyopathy: a comparison of patients with and without postprandial exacerbation of symptoms. *Clin Cardiol*. 1996;19:129–135.
  54. Feiner E, Arabadjian M, Winson G, Kim B, Chaudhry F, Sherrid MV. Postprandial upright exercise echocardiography in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;61:2487–2488.
  55. Paz R, Jortner R, Tunick PA, Sclarovsky S, Eilat B, Perez JL, Kronzon I. The effect of the ingestion of ethanol on obstruction of the left ventricular outflow tract in hypertrophic cardiomyopathy. *N Engl J Med*. 1996;335:938–941.
  56. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodríguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*. 2003;289:2363–2369.
  57. Maron MS, Olivetto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, Haas TS, Udelson JE, Manning WJ, Maron BJ. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. *Circulation*. 2011;124:40–47.
  58. El Sabbagh A, Newman DB, Miranda WR, Nishimura RA. Hypertrophic obstructive cardiomyopathy and uncontrolled hypertension: a therapeutic challenge. *JACC Cardiovasc Interv*. 2016;9:e3–e4.
  59. Argulian E, Messerli FH, Aziz EF, Winson G, Agarwal V, Kaddaha F, Kim B, Sherrid MV. Antihypertensive therapy in hypertrophic cardiomyopathy. *Am J Cardiol*. 2013;111:1040–1045.
  60. van Dockum WG, Beek AM, ten Cate FJ, ten Berg JM, Bondarenko O, Götte MJW, Twisk JWR, Hofman MBM, Visser CA, van Rossum AC. Early onset and progression of left ventricular remodeling after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. *Circulation*. 2005;111:2503–2508.
  61. El-Hamamsy I, Lekadir K, Olivetto I, El Guindy A, Merrifield R, Rega L, Yang G, Cecchi F, Yacoub MH. Pattern and degree of left ventricular remodeling following a tailored surgical approach for hypertrophic obstructive cardiomyopathy. *Glob Cardiol Sci Pract*. 2012;2012:9.
  62. Marian AJ, Yu QT, Workman R, Greve G, Roberts R. Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. *Lancet*. 1993;342:1085–1086.
  63. Perkins MJ, Van Driest SL, Ellsworth EG, Will ML, Gersh BJ, Ommen SR, Ackerman MJ. Gene-specific modifying effects of pro-LVH polymorphisms involving the renin-angiotensin-aldosterone system among 389 unrelated patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2005;26:2457–2462.
  64. Olivetto I, Maron BJ, Tomberli B, Appelbaum E, Salton C, Haas TS, Gibson CM, Nistri S, Servettini E, Chan RH, Udelson JE, Lesser JR, Cecchi F, Manning WJ, Maron MS. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;62:449–457.
  65. de Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M. Obesity and cardiac function. *Circulation*. 1981;64:477–482.
  66. Canepa M, Sorensen LL, Pozios I, Dimaano VL, Luo HC, Pinheiro AC, Strait JB, Brunelli C, Abraham MR, Ferrucci L, Abraham TP. Comparison of clinical presentation, left ventricular morphology, hemodynamics, and exercise tolerance in obese versus nonobese patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2013;112:1182–1189.
  67. Chiuvè SE, Sun Q, Sandhu RK, Tedrow U, Cook NR, Manson JE, Albert CM. Adiposity throughout adulthood and risk of sudden cardiac death in women. *JACC Clin Electrophysiol*. 2015;1:520–528.
  68. Nerbass FB, Pedrosa RP, Danzi-Soares NJ, Drager LF, Arteaga-Fernández E, Lorenzi-Filho G. Obstructive sleep apnea and hypertrophic cardiomyopathy: a common and potential harmful combination. *Sleep Med Rev*. 2013;17:201–206.
  69. Eleid MF, Konecny T, Orban M, Sengupta PP, Somers VK, Parish JM, Mookadam F, Brady PA, Sullivan BL, Khandheria BK, Ommen SR, Tajik AJ. High prevalence of abnormal nocturnal oximetry in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009;54:1805–1809.
  70. Pedrosa RP, Drager LF, Genta PR, Amaro ACS, Antunes MO, Matsumoto AY, Arteaga E, Mady C, Lorenzi-Filho G. Obstructive sleep apnea is common and independently associated with atrial fibrillation in patients with hypertrophic cardiomyopathy. *Chest*. 2010;137:1078–1084.
  71. Raphael CE, Cooper R, Parker KH, Collinson J, Vassiliou V, Pennell DJ, de Silva R, Hsu LY, Greve AM, Nijjer S, Broyd C, Ali A, Keegan J, Francis DP, Davies JE, Hughes AD, Arai A, Frenneaux M, Stables RH, Di Mario C, Prasad SK. Mechanisms of myocardial ischemia in hypertrophic cardiomyopathy: insights from wave intensity analysis and magnetic resonance. *J Am Coll Cardiol*. 2016;68:1651–1660.
  72. Maron MS, Olivetto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, Camici PG. The case for myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009;54:866–875.
  73. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. *Circulation*. 2003;108:2342–2348.
  74. Basso C, Thiene G, Mackey-Bojack S, Frigo AC, Corrado D, Maron BJ. Myocardial bridging, a frequent component of the hypertrophic cardiomyopathy phenotype, lacks systematic association with sudden cardiac death. *Eur Heart J*. 2009;30:1627–1634.
  75. Olivetto I, Cecchi F, Bini R, Favilli S, Murzi B, El-Hamamsy I, Yacoub MH. Tunneled left anterior descending artery in a child with hypertrophic cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2009;6:134–139.
  76. Dhandapani PS, Sadyappan S, Xue Y, Powell GT, Rani DS, Nallari P, Rai TS, Khullar M, Soares P, Bahl A, Tharkan JM, Vaideswar P, Rathinavel A,

- Narasimhan C, Ayapati DR, Ayub Q, Mehdi SQ, Oppenheimer S, Richards MB, Price AL, Patterson N, Reich D, Singh L, Tyler-Smith C, Thangaraj K. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. *Nat Genet*. 2009;41:187–191.
77. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J, McNamara DM, Seidman CE, Seidman JG, Arany Z; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med*. 2016;374:233–241.
78. Helms AS, Davis FM, Coleman D, Bartolone SN, Glazier AA, Pagani F, Yob JM, Sadayappan S, Pedersen E, Lyons R, Westfall MV, Jones R, Russell MW, Day SM. Sarcomere mutation-specific expression patterns in human hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. 2014;7:434–443.
79. Roncarati R, Viviani Anselmi C, Losi MA, Papa L, Cavarretta E, Da Costa Martins P, Contaldi C, Saccani Jotti G, Franzone A, Galastri L, Latronico MV, Imbriaco M, Esposito G, De Windt L, Betocchi S, Condorelli G. Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2014;63:920–927.
80. Wang RS, Maron BA, Loscalzo J. Systems medicine: evolution of systems biology from bench to bedside. *Wiley Interdiscip Rev Syst Biol Med*. 2015;7:141–161.

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