

CONTEMPORARY REVIEW

Unraveling the Genotype-Phenotype Relationship in Hypertrophic Cardiomyopathy: Obesity-Related Cardiac Defects as a Major Disease Modifier

Edgar E. Nollet , MSc; B. Daan Westenbrink , MD, PhD; Rudolf A. de Boer , MD, PhD; Diederik W. D. Kuster , PhD; Jolanda van der Velden , PhD

ABSTRACT: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy and is characterized by asymmetric septal thickening and diastolic dysfunction. More than 1500 mutations in genes encoding sarcomere proteins are associated with HCM. However, the genotype-phenotype relationship in HCM is incompletely understood and involves modification by additional disease hits. Recent cohort studies identify obesity as a major adverse modifier of disease penetrance, severity, and clinical course. In this review, we provide an overview of these clinical findings. Moreover, we explore putative mechanisms underlying obesity-induced sensitization and aggravation of the HCM phenotype. We hypothesize obesity-related stressors to impact on cardiomyocyte structure, metabolism, and homeostasis. These may impair cardiac function by directly acting on the primary mutation-induced myofilament defects and by independently adding to the total cardiac disease burden. Last, we address important clinical and pharmacological implications of the involvement of obesity in HCM disease modification.

Key Words: disease modifiers ■ hypertrophic cardiomyopathy ■ obesity ■ pathophysiology ■ type 2 diabetes mellitus

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, with an estimated prevalence of 1:500 to 1:200 and a frequent cause of sudden cardiac death in young individuals.¹ HCM is clinically defined by increased left ventricular (LV) wall thickness (>15 mm) that cannot be attributed solely to abnormal loading conditions.² The most prominent clinical features of HCM include LV outflow tract obstruction caused by asymmetric septal thickening and diastolic dysfunction.² Histological analyses of cardiac tissue from patients with HCM show cardiomyocyte hypertrophy and disarray, fibrosis, and reduced capillary density.³⁻⁵ In 50% to 60% of all patients with HCM, a pathogenic variant (mutation) is found in genes encoding sarcomeric proteins, the contractile machinery of cardiomyocytes. In this

case, patients are termed genotype positive. Over 1500 mutations have been identified to be associated with HCM, most of which affect thick-filament genes (*MYH7*, *MYBPC3*, *MYL2*, and *MYL3*) and to a lesser extent thin-filament genes (*TNNT2*, *TNNI3*, *TPM1*, and *ACTC1*).⁶⁻⁸ As the vast majority of genotype-positive patients carries a heterozygous mutation, HCM is considered to be an autosomal dominant disease. It must be noted that the number of identified gene variants of unknown significance increased as a result of the larger diagnostic gene panels in clinical practice.^{9,10} These newly identified variants of unknown significance may be pathogenic or rather be a disease modifier. Understanding the exact contribution to HCM pathophysiology of newly identified gene variants is part of ongoing research. In the current review, we

Correspondence to: Jolanda van der Velden, PhD, De Boelelaan 1118 O2 Science Building 11W53, 1081 HZ Amsterdam, The Netherlands. E-mail: j.vandervelden1@amsterdamumc.nl

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Nonstandard Abbreviations and Acronyms

BCAA	branched chain amino acid
DM-II	type 2 diabetes mellitus
HCM	hypertrophic cardiomyopathy ; mTOR, mechanistic target of rapamycin
mTOR	mechanistic target of rapamycin
NYHA	New York Heart Association
ROS	reactive oxygen species
SGLT2i	sodium-glucose cotransporter 2 inhibitors

focus on established pathogenic variants, and use the term mutation.

Whereas it is well established that HCM is caused by sarcomere mutations, the phenotypical variation in terms of disease penetrance and severity is large in genotype-positive individuals; heterozygous mutation carriers may remain asymptomatic their entire life, while a first-degree relative may develop severe hypertrophy at a young age and may progress to end-stage heart failure (HF).^{2,11,12} Disease models are not ideal to recapitulate such heterogeneity: mouse models with a heterozygous sarcomere gene mutation do not develop a cardiac disease phenotype at young age, whereas homozygous mice show early and accelerated cardiac dysfunction.^{13–16} The latter pathogenic effect of sarcomere mutations is also evident from human cases with homozygous or compound heterozygous mutations that show severe cardiomyopathy at birth and death at childhood.^{17,18} These studies show that the dose of the mutant sarcomere protein, which is regulated at RNA and protein level, determines the onset and severity of cardiomyopathy.

Based on the observation that harboring a heterozygous mutation is by itself not sufficient to initiate and drive disease progression, it has been hypothesized that HCM development is tightly intertwined with additional or secondary disease-modifying factors.^{19–21} These additional disease hits may either directly aggravate mutation-related dysfunction by affecting the cell systems that maintain cardiomyocyte homeostasis aimed to prevent accumulation of mutant protein or impair cardiac function independently of mutation-related cardiomyocyte dysfunction.

Recent observations from studies of patients with HCM, including prospective cohort studies, suggest a role of known cardiovascular risk factors,²² most notably obesity, in disease penetrance and severity.^{21,23–34} In this review, we summarize these clinical findings and provide an overview of putative mechanisms that may underlie obesity-related aggravation of the HCM phenotype.

CLINICAL REPORTS ON THE IMPACT OF OBESITY ON HCM PREVALENCE, PHENOTYPE, AND OUTCOME

In recent years, cohort studies yielded significant insight in the involvement of obesity in phenotypic expression of HCM (Figure 1). High prevalence of obesity in patients with HCM was reported by Reineck and colleagues.²⁴ In patients with HCM who responded to a survey of health behaviors, mean body mass index (BMI) was >30 kg/m² and prevalence of obesity was 43%, which are both significantly higher than in the general US population.²⁴ These findings were later confirmed in large-scale international multicenter registries of patients with HCM (ie, the SHaRe

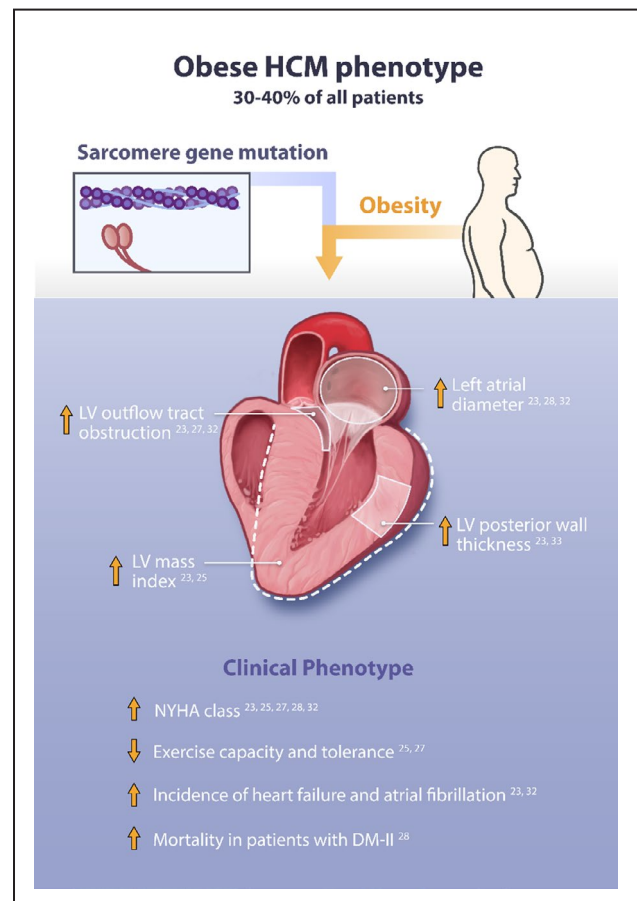


Figure 1. Summary of structural and clinical features of the obese hypertrophic cardiomyopathy (HCM) phenotype.

Obesity in patients with HCM is associated with increased prevalence of left ventricular (LV) outflow tract obstruction, left atrial enlargement, a higher LV mass index, and increased LV posterior wall thickness. Clinically, obese patients with HCM present with worse New York Heart Association (NYHA) class symptoms and reduced exercise capacity and tolerance compared with lean patients. Incidence of heart failure and atrial fibrillation during follow-up is higher in obese patients with HCM than in lean patients. Patients with HCM with type 2 diabetes mellitus (DM-II) display increased mortality compared with nondiabetic patients with HCM.

[Sarcomeric Human Cardiomyopathy Registry] [mean BMI=28 kg/m²; obesity prevalence=32%] and the HCMR [Hypertrophic Cardiomyopathy Registry] [mean BMI=29 kg/m²; obesity prevalence=38%].^{32,33} This raises the question whether obesity adversely modifies HCM disease expression, or rather is a reflection of an increase in sedentary behavior after diagnosis.³⁵ Indeed, although patients with HCM are advised to regularly perform nonstrenuous exercise,^{2,36} most patients indicate they do not meet physical activity recommendations because of physical discomfort, fear of sudden cardiac death, or misinterpreted medical advice.^{24,37}

The hesitance of patients to perform physical activity may thus contribute to the observed increase in body weight, and the sedentary lifestyle may thereby have a negative impact on disease progression. Recent evidence specifically supports the potential of high body weight to adversely predispose individuals to develop HCM.^{29,30,34} The nationwide register-based prospective cohort studies in Sweden observed that high BMI in young adulthood was a predictor of developing HCM or other cardiomyopathies later in life. Among men conscripted for military service, obesity displayed a hazard ratio (HR) of 3.17 to 3.39 for being diagnosed with HCM compared with lean body weight.²⁹ Strikingly, each 1-unit increase in BMI was associated with a 9% increase in the risk of being diagnosed with HCM.²⁹ In women of childbearing age, obesity was associated with a nearly 3 times higher risk (HR, 2.60–2.77) versus normal BMI, and a 6% increase per 1-unit increase in BMI was reported.³⁰ As pointed out by the authors, the finding that high BMI before disease onset is associated with a greater chance of being diagnosed with HCM in late adulthood implies that obesity-induced cardiac stress may sensitize and aggravate mutation-induced myocardial defects, resulting in phenotypic expression of HCM.³⁰ Similar findings were reported in a recent study using nationwide population-based data from the Korean National Health Insurance Service.³⁴ Over a median follow-up of 5.2 years, individuals with a BMI >30 kg/m² had a 3 times higher risk (HR, 3.00) of being diagnosed with HCM compared with lean individuals, and each 1-unit increase in BMI displayed an 11% risk increase.

In addition to modifying disease penetrance, obesity is associated with a worse phenotype and clinical course, as demonstrated by several studies.^{23,25–27,31–33} In terms of clinical presentation, obese patients with HCM display notably differing functional and morphological features compared with lean patients with HCM (summarized in Table 1 and Figure 1). Obese patients with HCM are more symptomatic, as evaluated by New York Heart Association (NYHA) functional class, but also present more frequently with a significant LV outflow tract obstruction.^{23,25,27,32} The functional limitation

in obese patients with HCM is also manifested by lower exercise tolerance and capacity compared with non-obese patients.^{25,27} Moreover, obesity is associated with a higher LV mass index, LV cavity enlargement, larger left atrial diameter, and greater posterior wall thickness.^{23,25,27,38} The latter is also observed in obese pediatric patients with HCM.³¹ With respect to the association between BMI and maximal LV wall thickness (ie, typically septal thickness), the studies cited here suggest a modest impact of obesity, requiring vast sample sizes for detection.^{32,33} No difference was reported in ejection fraction between obese and lean patients with HCM.^{23,25,27,32}

Two studies have described associations between BMI and (long-term) clinical outcomes.^{23,32} Olivotto and colleagues report no difference in survival between lean and obese patients during a median follow-up of 3.7 years. However, obesity was found to be an independent predictor (HR, 3.6) of developing NYHA ≥III functional class symptoms.²³ Also, in a larger cohort with a median follow-up of 6.8 years, Fumagalli et al found higher incidence of NYHA ≥III symptoms at last visit (10% versus 16%; $P<0.001$) and atrial fibrillation during follow-up (19% versus 24%; $P=0.03$) in obese compared with lean patients with HCM.³² Compared with lean patients, obese patients more often developed the HF composite outcome (defined as LV ejection fraction <35%, development of NYHA class III/IV symptoms, cardiac transplant, or LV assist device implantation³⁹; lean 19% versus obese 30%; $P<0.001$). In addition, compared with lean patients, obese patients more frequently developed the HCM-related overall composite outcome (defined as first occurrence of any ventricular arrhythmic event or HF composite end point [without inclusion of LV ejection fraction], all-cause mortality, atrial fibrillation, and stroke³⁹; lean 42% versus obese 55%; $P<0.001$).³² Moreover, obesity was independently also positively associated with the HF composite outcome (HR, 1.89) and the HCM-related overall composite outcome (HR, 1.63).³² Occurrence of ventricular arrhythmias did not display an association with obesity, suggesting that obese patients with HCM are not at increased risk of sudden cardiac death. However, the authors emphasize that, because of low event rates, longitudinal follow-up studies are needed to draw definite conclusions about arrhythmic risk in obese patients with HCM.^{32,39}

Of note, in the general population, obesity is associated with other cardiovascular risk factors, such as hypertension and type 2 diabetes mellitus (DM-II).^{22,40} Increased prevalence of these conditions by BMI group is also a universal finding in the clinical reports discussed here. However, it was not reported or, because of small sample sizes, not possible to thoroughly study how hypertension and DM-II may independently influence baseline clinical phenotype and disease course.

Table. Baseline Characteristic of Patients With HCM in Obesity- and Diabetes Mellitus-Related Studies

Study	No. of Patients	BMI, kg/m ²	Obesity, %	Patient Group Comparison	No. per Group	% of Patients With NYHA class ≥II or ≥III Symptoms	EF, %	% of Patients With Inducible LVOTO	LVMI		LAD		Maximum LVWT, mm	PWT, mm
									g/m ²	...	mm	...		
23	275	29	37	BMI <25 kg/m ² vs BMI >30 kg/m ²	69-101	32-35	71-72	22-50*	g/m ²	96-114*	mm	42-46*	22-21	...
27	510	30	45		90-228	33-46	70-70	62-71*	17-17	12-13*
32	3282	28	32		962-1040	9-21*	65-66	21-32*	mm	42-48*	17-18*	...
33	2580	29	38		611-984	20-21*	...
25	242	30	36	BMI <30 kg/m ² vs BMI >30 kg/m ²	154-88	30-49*	66-65	33-46	g/m ² :7	58-67*	21-21	11-12*
28	294	No DM-II vs DM-II	194-100	66-87*	67-69	% of Patients with LAD ≥40 mm	75-86*	17-18	12-12

Values represent means or percentages if indicated. BMI indicates body mass index; DM-II, type 2 diabetes mellitus; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LAD, left atrial diameter; LVMI, left ventricular mass index; LVOTO, left ventricular outflow tract obstruction; LVWT, left ventricular wall thickness; NYHA, New York Heart Association; and PWT, posterior wall thickness.
*Significant differences.

Nevertheless, higher BMI has been associated with new-onset HF, regardless of etiology.⁴¹ Solely with respect to LV mass index and exercise tolerance an independent positive association with hypertension was demonstrated.^{23,25} Evidence supporting a negative impact of obesity-related cardiovascular risk factors on HCM disease expression and progression comes from 3 studies.^{21,28,34} The Korean nationwide study addressing the relationship between BMI and HCM diagnosis during follow-up substratified 3 BMI groups (<23, 23.0–24.9, and >25 kg/m²) by metabolic status (ie, metabolically healthy versus metabolically unhealthy, as defined by presence of hypertension, hyperlipidemia, or diabetes mellitus).^{34,42} In each BMI group, it was observed that metabolically unhealthy participants had an approximately 1.5 times higher HR for being diagnosed with HCM compared with metabolically healthy participants. In a cohort of *MYL2* mutation carriers (n=38), hypertension was a strong independent risk factor for HCM manifestation. Moreover, presence of any risk factor for hypertrophy, such as obesity, was found in 89% of all patients.²¹ The impact of DM-II on clinical phenotype and outcome (Table 1) was studied in a matched cohort composed of diabetic and nondiabetic patients with HCM from Spanish and Israeli referral centers (n=294).²⁸ Compared with nondiabetic patients, diabetic patients with HCM more often displayed left atrial enlargement, diastolic dysfunction, and mitral regurgitation. Patients with HCM with DM-II additionally displayed worse NYHA functional class symptoms and lower exercise capacity. No significant differences were reported with respect to ventricular arrhythmic events in patients with HCM with DM-II. Clinical course was reported to be more severe in diabetic patients with HCM, as evidenced by a significantly higher 15-year mortality rate (non-DM-II 15% versus DM-II 22%; *P*=0.03, log-rank test).²⁸

Taken together, these studies display a clear negative impact of obesity, and its associated comorbidities, on HCM disease expression and progression. The question that therefore arises concerns the mechanisms by which obesity impacts on cardiac function, causing this phenomenon. Because obesity is known to drive LV hypertrophy and diastolic dysfunction in the general population,⁴³ it may be hypothesized that obesity promotes phenotypic expression and progression of HCM by impairing cardiac function in parallel with mutation-induced impairments. Alternatively, or in addition, obesity-related myocardial stress may drive HCM by enhancing mutation-induced pathogenic effects.

SARCOMERE INEFFICIENCY AT THE BASIS OF HCM PATHOGENESIS

A brief overview of the current understanding of the pathophysiology of HCM is required to interpret clinical

findings that identified obesity as an important risk factor for developing cardiomyopathy.

A range of functional changes have been described as a consequence of sarcomere mutations, which are schematically depicted in Figure 2 and briefly summarized in the following paragraph. Mutations in sarcomere proteins cause increased Ca^{2+} sensitivity of the myofilaments, increased tension cost,^{16,44–49} and altered myosin sequestration,^{50,51} which together lead to increased ATP use. Increased Ca^{2+} sensitivity induces myofilament activation at relatively low Ca^{2+} levels and delays the dissociation of Ca^{2+} from cardiac troponin C, resulting in prolonged cross-bridge activation and impaired relaxation. Increased tension cost entails that in HCM cardiomyocytes more ATP is hydrolyzed to generate the same amount of force compared with healthy cardiomyocytes. Altered myosin sequestration refers to a smaller portion of

myosins achieving the superrelaxed state conformation during diastole, which is associated with increased ATPase activity at low $[Ca^{2+}]$ and prolonged duration of relaxation. Increased ATP consumption caused by sarcomere mutations has been proposed to propel HCM development via several self-reinforcing mechanisms.^{19,52–56} Elevated ADP levels as a result of ATP depletion are thought to play a pivotal role herein. High ADP levels directly stimulate mitochondrial ATP regeneration,⁵⁷ which in the healthy heart is accompanied by increased mitochondrial calcium uptake to boost activity of the Krebs cycle needed to fuel ATP regeneration and detoxify concomitant reactive oxygen species (ROS) formation.^{58,59} In HCM, it has been postulated that high mitochondrial workload caused by ATP depletion is not matched by a proper increase in mitochondrial $[Ca^{2+}]$ due to Ca^{2+} sequestration in the myofilaments.⁵⁶ Reductions in

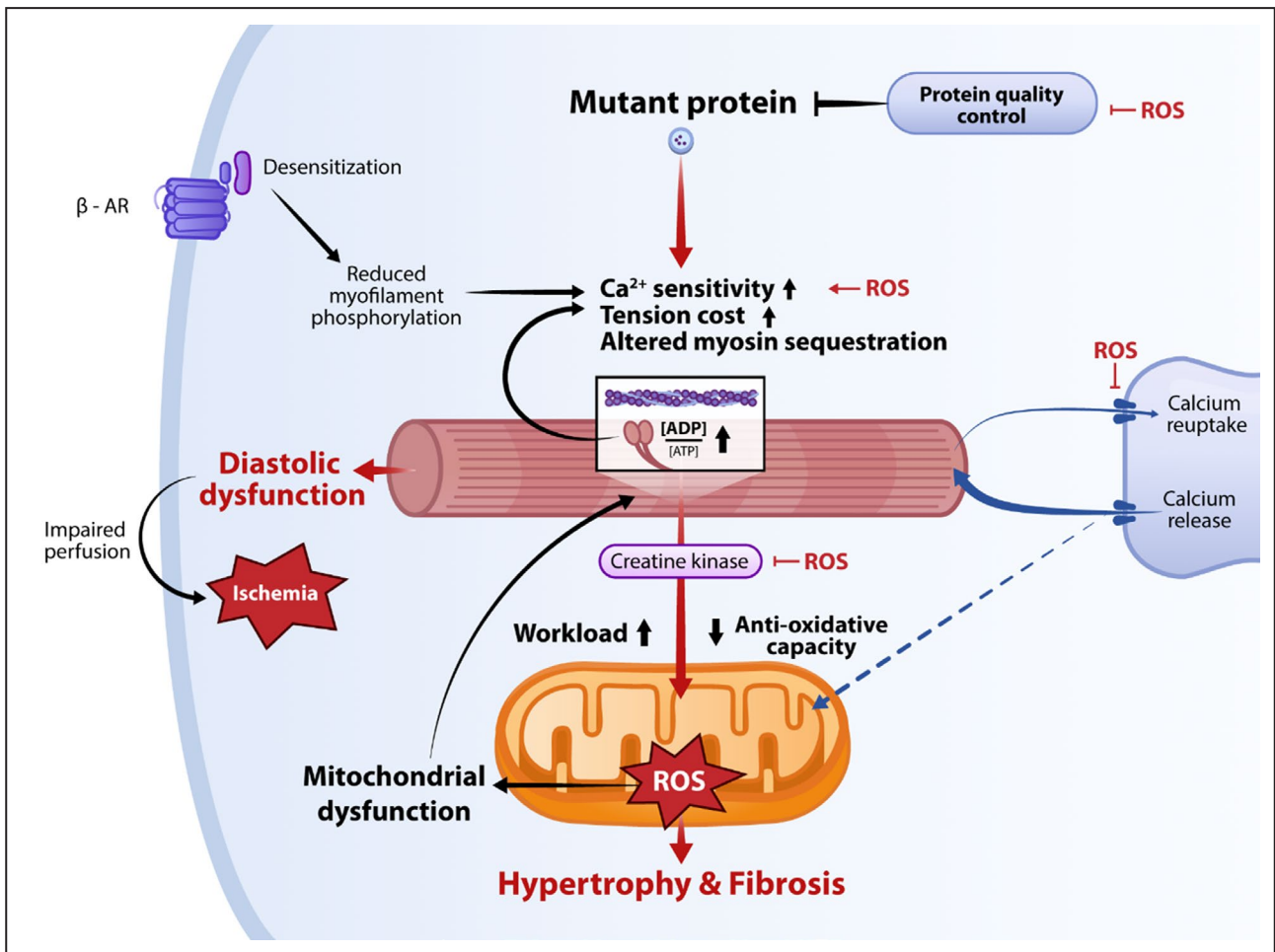


Figure 2. Proposed pathophysiology of hypertrophic cardiomyopathy.

Mutant protein gives rise to sarcomere inefficiency, disturbed calcium homeostasis, and diastolic dysfunction. This evokes mitochondrial dysfunction and oxidative stress, raising mutant protein levels via inhibition of protein quality control mechanisms, which aggravates cardiomyocyte dysfunction. This self-reinforcing feedback loop ultimately promotes prohypertrophic and fibrotic cardiac remodeling. During disease development, desensitization of the β -adrenergic receptor (β -AR) occurs, which causes reduced myofilament protein phosphorylation and contributes to sarcomere dysfunction. See main text for a more elaborate description. ROS indicates reactive oxygen species.

mitochondrial $[Ca^{2+}]$ will reduce antioxidative capacity and affect the ability to adequately buffer ADP.⁵⁶ Increased ROS production and reduced antioxidative capacity give rise to excessive ROS levels and culminate in oxidative stress, damaging macromolecules and organelles and adversely modifying a plethora of redox-sensitive signaling pathways and proteins that potentially drive HCM disease progression.¹⁹ In brief, oxidative stress and concomitant oxidative modifications may (1) decrease functioning of the creatine kinase shuttle, further lowering ADP-buffering capacity⁶⁰; (2) increase Ca^{2+} sensitivity and hamper relaxation (ie, diastolic dysfunction) of the myofilaments^{61,62}; (3) disturb Ca^{2+} cycling, resulting in reduced Ca^{2+} reuptake^{63,64}; (4) impair mitochondrial function by modification of complex proteins,⁶⁵ lipid damage (eg, cardiolipin peroxidation^{66,67}), and mitochondrial DNA damage^{68,69}; and (5) induce ubiquitin-proteasome system dysfunction and endoplasmic reticulum stress, raising mutant protein dose.^{70–72} These pathogenic effects further disrupt myofilament function and/or contribute to ROS production, disturbing cardiomyocyte homeostasis and inducing prohypertrophic and fibrotic signaling. The apparent observation of higher mutant protein levels at more advanced disease stages is in line with such a feed-forward mechanism in HCM pathophysiology.⁷³

A particularly pathogenic factor in HCM disease progression that needs to be highlighted here is diastolic dysfunction. Diastolic dysfunction may initially be caused by relatively high cross-bridge activity during diastole as a result of increased myofilament Ca^{2+} sensitivity, and likely worsened through ADP-mediated Ca^{2+} sensitization,⁷⁴ oxidative stress,⁶² and reduced β -adrenergic receptor signaling.^{75,76} Severe diastolic dysfunction may cause microvascular dysfunction, as coronary perfusion takes place during diastole,⁷⁷ and ultimately leads to local ischemia, tissue death, and replacement fibrosis, which dramatically alters the already disturbed redox balance in cardiomyocytes.⁷⁸

In summary, energetic and metabolic stress appears to be a central consequence of the sarcomere mutation-induced cardiomyocyte defects.

OBESITY IN HCM: PARALLEL OR ENHANCING EFFECT?

As mentioned, obesity may impact on HCM phenotype and disease course by affecting cardiac function independently of mutation-induced effects, adding to the total cardiac disease burden, whereas it can also be hypothesized that obesity enhances mutation-induced pathogenic effects. The general finding of a positive association between BMI and NYHA class^{25,28,32} is for

example also observed in patients with HF with preserved ejection fraction,⁷⁹ thus not necessarily suggesting a direct impact of obesity on mutation-related defects in HCM.

In the general population (ie, in the absence of HCM), cardiac remodeling associated with obesity is predominantly reflected by higher LV mass index, larger LV cavity size, and diastolic dysfunction.⁴³ Also in patients with HCM, the most notable impact of obesity appears to be higher LV mass index, LV cavity enlargement, and worse diastolic dysfunction, the latter being reflected by a larger left atrial diameter.^{23,25,32} These findings seem to argue mostly in favor of a parallel effect of obesity on the HCM myocardium. However, Rayner and colleagues recently reported that in HCM the degree of LV cavity dilatation associated with increasing BMI was 2-fold larger than in nondiseased hearts.³⁸ In addition, the increase in LV mass index associated with an increase in BMI was higher in hearts with HCM compared with nondiseased hearts (1.3 versus 2.3 g/kg per m^2 , respectively), although the difference in slope was not statistically significant ($P=0.10$). The finding that the heart with HCM seems to dilate excessively to increase stroke volume might suggest that the presence of a sarcomere mutation diminishes the capacity of the myocardium to cope with obesity-related increased physiological demand and stress.

In addition, LV outflow tract obstruction, a characteristic feature of HCM, is more common in obese patients with HCM.^{23,25,27,32} As obesity is related with increased LV mass, the typical asymmetric septal hypertrophy may be more severe in obese than in lean patients with HCM. However, clinical studies on the impact of obesity on HCM report either no or only a modest difference in septal thickness between lean and obese patients.^{23,25,27,32,33} In fact, in a subpopulation of patients with HCM with a (likely) pathogenic mutation ($n=1035$), Fumagalli and colleagues report no effect of obesity on maximal LV wall thickness. The mean maximal septal thickness in the aforementioned genotype-positive cohort was relatively high (20 mm), which may indicate that septal remodeling was already too advanced to detect a large obesity-mediated effect on LV mass.³² Interestingly, in a small cohort ($n=32$) with a mean maximal septal thickness of 17 mm, a positive association was found between septal thickness and truncal fat.²⁶ However, the number of genotype-positive patients was not reported in this study; thus, it remains unclear if the observed association would hold true in a strictly genotype-positive patient population. Of note, the overall positive association between BMI and maximal LV wall thickness reported by Fumagalli et al was ascribed to observations made in mutation-negative patients with HCM,³² suggesting a direct influence of

obesity on septal thickness in the absence of sarcomeric mutations. Notable differences in cardiac remodeling and morphological features have recently been reported between sarcomere mutation-positive and mutation-negative patients with HCM,³³ warranting further study into the mechanisms underlying this phenomenon. Taken together, assessment of the role of obesity on cardiac remodeling in genotype-positive individuals is challenging, and warrants prospective follow-up studies in genotype-positive, phenotype-negative mutation carriers.

OBESITY-RELATED CARDIAC DEFECTS AS SECOND DISEASE HIT IN HCM: POSSIBLE PATHOMECHANISMS

Obesity and its associated comorbidities may induce and aggravate HCM via multiple mechanisms that have been described in obesity-related cardiac dysfunction and diabetic cardiomyopathy, and range from vascular dysfunction to structural changes and perturbations in cardiomyocyte homeostasis and metabolism. We provide an overview of described mechanisms, with a possible link to HCM. The proposed interplay of obesity-related cardiac defects and mutation-induced pathomechanisms is schematically visualized in Figure 3.

Endothelial Dysfunction and Inflammation

We put forward that endothelial dysfunction and inflammation may be important mediators that aggravate cardiomyocyte dysfunction in HCM pathophysiology. It has been proposed that a systemic proinflammatory state caused by comorbidities, such as obesity and diabetes mellitus, underlies endothelial dysfunction.⁸⁰ In brief, microvascular endothelial inflammation stimulates profibrotic signaling by fibroblasts and induces cardiomyocyte stiffness and hypertrophy via reduced NO bioavailability and protein kinase G activity. The net result thereof is hypertrophic remodeling, diastolic dysfunction, and impaired coronary flow reserve,⁸¹ contributing to HCM pathophysiological features in several ways. As highlighted earlier, diastolic dysfunction and reduced coronary perfusion may be particularly pathogenic in HCM disease progression because of their redox-disturbing and ischemic effects. Vascular dysfunction has been observed in hearts of patients with HCM, in particular in patients with a gene mutation, and is thought to precede development of cardiac hypertrophy, as evidenced by blunted coronary flow in response to adenosine in nonhypertrophied regions of the heart.^{82–85} Extrinsic factors contributing

to microvascular dysfunction may thus bear exceptional potential to set off pathologic remodeling in HCM. Intriguingly, the notion of vascular dysfunction especially in mutation-positive patients, implies that presence of mutant protein causes vascular remodeling (eg, via oxidative stress-induced profibrotic signaling), resulting in increased adventitial collagen deposition.^{19,86,87} Oxidative stress as a result of NO synthase uncoupling and nicotinamide adenine dinucleotide phosphate oxidase activity in endothelial dysfunction may increase mutant protein dose via ubiquitin-proteasome system dysfunction,^{70,88,89} and therefore possibly represents a self-reinforcing mechanism through which endothelial dysfunction and disturbed cardiomyocyte homeostasis impact on one another.

Cardiac adiposity may represent an important mediator of local myocardial inflammation and endothelial dysfunction. Recent studies suggest the existence of direct interactions between epicardial adipose tissue and the myocardium,^{90,91} and abdominal adiposity has been associated with new-onset HF.⁹² The epicardial fat volume was associated with the degree of cardiac hypertrophy and severity of diastolic dysfunction, and circulating biomarkers related to myocyte injury.⁹⁰ These findings indicate that there is direct communication between epicardial fat and the myocardium. Myocardial lipid accumulation has been recognized as a source of proinflammatory adipokines and cytokines,⁹³ contributing to impaired vasodilation, cardiac stiffening, and remodeling, and is associated with lipotoxicity, which is detrimental to cardiomyocyte homeostasis.⁹⁴ The association between obesity and the onset and progression of HCM therefore may be explained by myocardial adiposity, either through interactions between epicardial fat and the myocardium or rather by direct intramyocardial accumulation of fat.⁹⁵ Clearly, comprehensive knowledge on the role of obesity-related systemic changes and coincident endothelial dysfunction and inflammation in the development of HCM is absent, and warrants research.

Obesity-Induced Hemodynamic Alterations and Cardiac Hypertrophy

Obesity is characterized by changes in hemodynamics and cardiac remodeling,^{43,96} which hold several implications for the myocardium with HCM. Obesity is associated with increased LV mass and frequently displays concentric LV geometry.^{43,97} Hypertrophic stimuli driving LV remodeling may impact on cellular homeostasis and mechanisms aimed at preventing incorporation and accumulation of mutant protein, thereby eliciting mutation-related pathogenicity. For example, the mechanistic target of rapamycin (mTOR), a major regulator of protein synthesis and

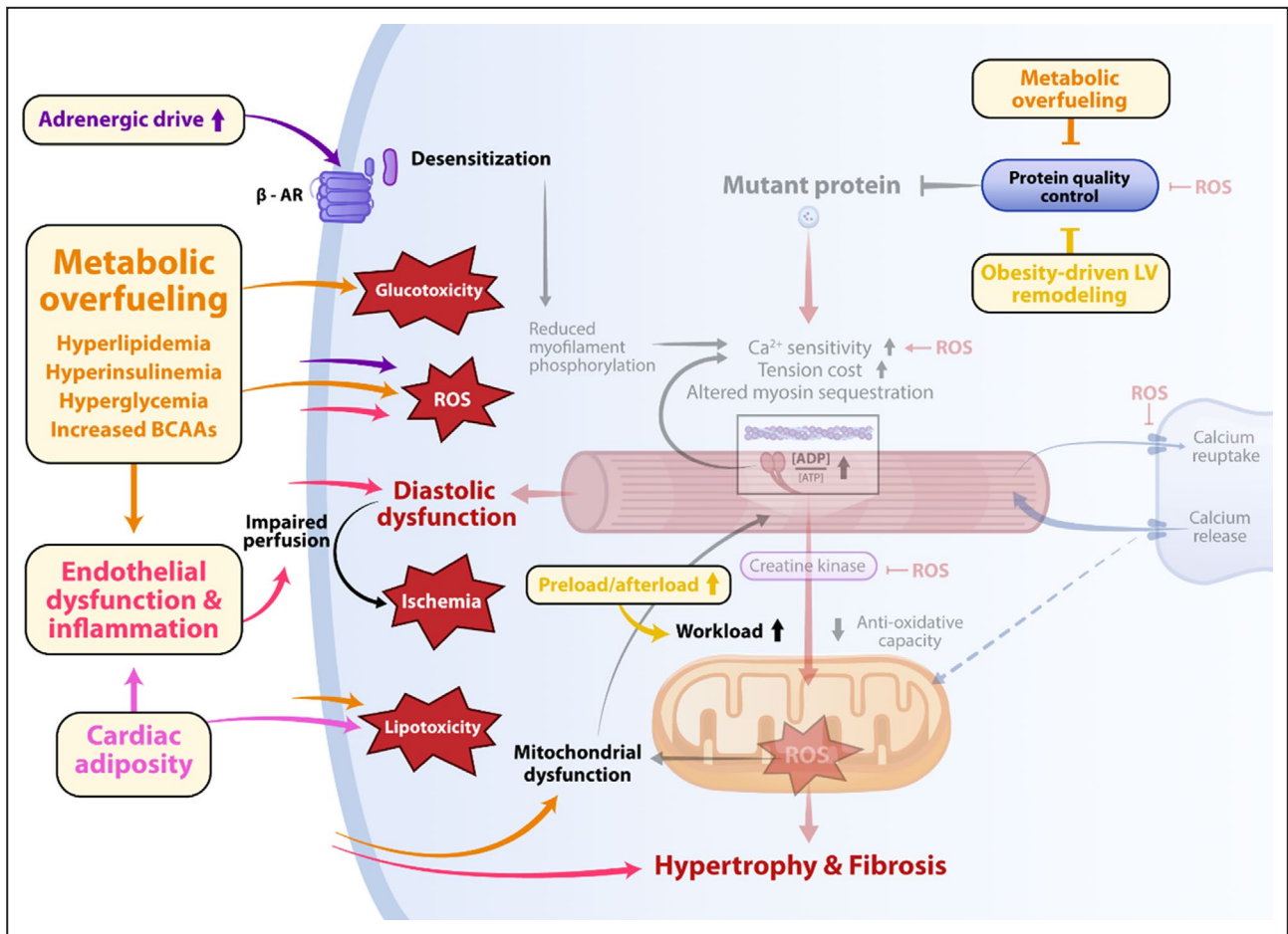


Figure 3. Overview of hypothesized obesity-related stressors affecting cardiomyocyte function in hypertrophic cardiomyopathy.

Increased adrenergic drive in obesity accelerates β -adrenergic receptor (β -AR) desensitization. Increased preload and/or afterload raise mitochondrial workload. Metabolic overfueling and cardiac adiposity promote endothelial dysfunction and inflammation, and induce lipotoxicity, glucotoxicity, and oxidative stress. Endothelial dysfunction and inflammation further raise oxidative stress, aggravate diastolic dysfunction and perfusion defects, and promote hypertrophy and fibrosis. Protein quality control is impaired by metabolic overfueling and left ventricular (LV) remodeling, raising mutant protein levels. BCAA indicates branched chain amino acid; and ROS, reactive oxygen species.

cardiomyocyte growth that is upregulated in DM-II and obesity, negatively modulates ubiquitin-proteasome system and autophagic activity.⁹⁸ In the HCM cardiomyocyte, this would entail increased production of mutant protein, but reduced clearance, raising mutant protein dose. Interestingly, in a *MYBPC3*-targeted knock-in mouse model of HCM, activation of autophagy by rapamycin administration or caloric restriction improved disease phenotype,⁹⁹ highlighting the importance of proper proteostasis in preventing HCM disease development.

Moreover, in obese individuals, cardiac output and workload are elevated because of increased circulating blood volumes and, in the case of coinciding hypertension, increased afterload.^{43,100} Mutant protein-harboring cardiomyocytes in HCM are already faced with increased mitochondrial workload and concomitant

stress because of high ATP use by inefficient sarcomeres,^{16,44–51} which thus may be exacerbated by sustained elevated cardiac workload due to hemodynamic changes. In addition, missense mutations in HCM are characterized by impaired length-dependent activation,⁴⁴ which likely limits contractile reserve of the heart during episodes of augmented preload. Sustained obesity-induced preload elevation may therefore lower the threshold for compensatory hypertrophy in HCM. The correlation between septal thickness and amount of truncal fat, but not total body fat or epicardial fat in patients with HCM, observed by Guglielmi and colleagues, is in line with the notion of a hemodynamics-mediated effect on cardiac remodeling.²⁶ Interestingly, epicardial fat amount was associated with N-terminal prohormone of brain natriuretic peptide levels.²⁶ Together, these observations imply the

importance of both hemodynamic alterations and epicardial fat accumulation in phenotypical presentation of HCM.

Sympathetic Nervous System Activation in Obesity

Symptomatic HCM with LV outflow tract obstruction is characterized by a high adrenergic drive.^{101,102} Chronic β -adrenergic receptor overstimulation leads to receptor downregulation and desensitization of this pathway,⁷⁶ which accordingly is observed and reflected by several defects in HCM.^{44,48,101,102} In human myectomy tissue, low phosphorylation of cardiac troponin I, a downstream target of protein kinase A, was observed, which causes increased Ca^{2+} sensitivity and impaired length-dependent activation of the myofilaments.^{44,48,103,104} Studies in a mouse model of HCM revealed that this phenomenon may be explained by selective phosphorylation of protein kinase A targets under conditions of β -adrenergic desensitization.¹⁰⁵ These human and mouse studies led to the concept of defective β -adrenergic receptor signaling as an important second disease hit in HCM disease progression.¹⁹ In obese and diabetic individuals, overactivity of the sympathetic nervous system is a common feature.^{106,107} Thus, adrenergic receptor stimulation via this route may add up to the already increased adrenergic drive in HCM, leading to premature impairment of β -adrenergic signaling pathways and further deterioration of cardiomyocyte function. In addition, β -adrenergic stimulation has also been described to evoke oxidative stress,^{108,109} therefore representing an additional mechanism through which obesity-induced sympathetic nervous system activation may disrupt cardiomyocyte homeostasis.

Obesity-Related Changes in Cardiac Metabolism

Metabolic changes associated with obesity, such as altered substrate preference and presence of toxic metabolites and intermediates, represent additional mechanisms through which obesity may impact on HCM pathophysiology. In obese, and in particular in diabetic individuals, hyperlipidemia and hyperinsulinemia (ie, metabolic overfueling) result in an increased delivery of fatty acids to the myocardium.^{110–112} As a result, cardiac metabolism loses substrate flexibility and becomes more reliant on fatty acid oxidation, which may be detrimental to the heart in multiple aspects.^{113–115} Mitochondrial ATP production through fatty acid oxidation is less efficient than glucose oxidation in terms of the number of ATP molecules produced for each oxygen atom consumed (phosphate/oxygen ratio, 2.33 versus 2.53, respectively¹¹⁵); in the HCM cardiomyocyte,

such an imbalance in energy production may exacerbate mutation-related perturbations of the mitochondrial capacity to regenerate ATP. In addition, disproportionate fatty acid oxidation increases expression of uncoupling proteins,¹¹³ further compromising mitochondrial ATP production. Importantly, despite the increase in fatty acid oxidation compared with glucose oxidation, the uptake of fatty acids exceeds fatty acid oxidation capacity and results in the intracellular accumulation of lipids.¹¹⁶ These lipids can be converted into toxic lipid species (eg, diacylglycerol and ceramides), which cause lipotoxicity.^{115,117,118} Lipotoxicity is associated with numerous deleterious effects, such as oxidative stress, mitochondrial dysfunction, apoptosis, endoplasmic reticulum stress, and inflammation.^{94,119–121} In addition, lipid overload elevates the level of acetyl-CoA precursors,¹²² which has been observed in skeletal muscle in DM-II and obesity and in failing hearts.^{123,124} As pointed out by Fukushima and Lopaschuk,¹²⁵ this may depress autophagic activity in the heart, as increased acetyl-CoA negatively regulates autophagy.¹²⁶ As discussed above, inhibition of autophagy may reduce clearance of mutant protein, thus raising mutant protein levels. Obesity has also been associated with increases in epicardial and intramyocardial fat in patients with HF, suggesting that the lipid accumulation is a general pathological cardiac response.^{90,91,95}

Hyperglycemia-induced glucotoxicity may occur in obesity and in particular in DM-II, which could also contribute to disease progression in HCM. High glucose exposure further promotes oxidative stress via nicotinamide adenine dinucleotide phosphate oxidase activation and mitochondrial ROS formation.¹²⁷ Hyperglycemia moreover induces formation and myocardial deposition of advanced glycation end products, which promotes inflammation and diastolic dysfunction.^{128,129} Activation of the hexosamine biosynthetic and polyol pathways may in addition stimulate prohypertrophic signaling and oxidative stress.^{115,130,131} Last, the possible impact of branched chain amino acids (BCAAs) on cardiometabolic risk has recently gained interest.¹³² In obese and diabetic individuals, circulating BCAAs are typically increased because of dietary intake and may accumulate in the myocardium in the case of metabolic perturbations.¹³³ BCAAs have been hypothesized to promote ROS formation, proinflammatory signaling, and mTOR activation in the myocardium.^{133,134} Recent analyses in The Hong Kong Diabetes Register demonstrated circulating BCAA levels to be independently associated with incident HF in patients with DM-II,¹³⁵ warranting further study into the mechanisms by which BCAAs may affect the myocardium. Altogether, a wide variety of metabolic perturbations associated with obesity and DM-II may negatively impact on the HCM myocardium and thus

likely represents a major adverse modifier of HCM development and progression.

THERAPEUTIC AND CLINICAL IMPLICATIONS

Lifestyle Interventions

Currently, there are no pharmacological treatment options available to cure or prevent HCM, although (ongoing) clinical trials aimed at altering contractile abnormalities and improving metabolism show promise.^{136–138} Current treatment strategies predominantly include use of β -blockers and antiarrhythmic drugs and surgical myectomy to ameliorate LV outflow tract obstruction, which are thus mostly aimed at management of symptoms and complications.² The drastic impact of obesity and its associated comorbidities on the mutation-harboring myocardium described in this review highlights the importance of weight loss and control in the clinical management of HCM. Given the association between high BMI at young age and the risk of developing HCM later in life,^{29,30} maintaining a healthy body weight may prevent or delay symptomatic expression of HCM in a significant proportion of mutation carriers. Accordingly, weight loss could substantially improve the clinical course in obese individuals with manifest HCM. It has been well established that weight loss following diet and/or exercise improves functional capacity in HF patients with preserved ejection fraction.^{139,140} However, reports on the benefit of weight loss in HCM are lacking. At the moment, there is one case report that demonstrated a significant amelioration of the clinical phenotype and partial regression of cardiac hypertrophy following weight loss in a 17-year-old obese boy with apical HCM.¹⁴¹ Furthermore, studies testing the effect of exercise on the myocardium in patients with HCM are scarce, which is likely due to safety concerns about exercise in patients with HCM.¹⁴² Nonetheless, the limited number of studies report good safety of exercise and consistently observe a positive effect on functional capacity and clinical outcome.^{142–146} Cavigli and colleagues recently formulated several key recommendations for exercise in patients with HCM that reinforce the notion that exercise is safe and potentially beneficial for patients with HCM. Nevertheless, adequately powered clinical trials are required to determine the effect of exercise and weight loss on myocardial remodeling and clinical outcomes in patients with HCM.¹⁴²

Pharmacological Interventions

HCM With Diabetes Mellitus

Weight loss remains a core component of all lifestyle interventions in patients with DM-II as it improves

glycemic control and disease progression.^{147,148} The therapeutic effects of metformin, which has been the cornerstone of pharmacological treatment of DM-II for decades, are for instance strongly linked to its effects on weight loss.¹⁴⁹ The therapeutic landscape of DM-II has, however, dramatically changed in recent years following several large randomized outcome trials with sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 analogues. Both classes of drugs exert favorable effects on body weight and reduce the incidence of cardiovascular events and mortality in patients with DM-II.^{148,150,151} SGLT2i have also consistently been shown to reduce the incidence of HF hospitalizations in patients with or at high risk for cardiovascular disease.¹⁴⁸ Mechanistically, glucagon-like peptide 1 analogues and SGLT2i exert a variety of roughly comparable systemic effects, including improvements in glycemic control, endothelial function, and blood pressure. In addition, both drug classes restore myocardial glucose oxidation in the diabetic heart.^{150,151} Interestingly, effects of SGLT2i on glycemic control are modest, whereas their effects on the heart are profound and could involve direct cardiac effects.¹⁵¹ Indeed, SGLT2i attenuate cardiac remodeling, reduce oxidative stress, and improve mitochondrial function in diabetic and nondiabetic animals.^{151–153} Furthermore, SGLT2i increase the bioavailability of ketones and promote their cardiac use as an additional fuel source, thereby restoring cardiac ATP.^{151,153,154} Finally, SGLT2i reduce the volume of epicardial adipose tissue, which may provide benefit to the heart as epicardial adipose tissue is thought to contribute to cardiac dysfunction through multiple mechanisms.^{90,155} Glucagon-like peptide 1 analogues and SGLT2i are both recommended as possible first-line agents for the treatment of patients with DM-II at increased cardiovascular risk. These cardiometabolic effects of SGLT2i and to a lesser extent glucagon-like peptide 1 analogues suggest that they could also exert beneficial effects on the energy-depleted myocardium in patients with HCM. SGLT2i also reduce the incidence of HF hospitalizations, and patients with HCM are at increased risk of developing HF. One might thus argue that SGLT2i should be preferred as the treatment of choice for DM-II in patients with HCM. Evidence to support this concept is currently unavailable.

HCM Without Diabetes Mellitus

There are no evidence-based pharmacological therapies that target obesity-related cardiac defects in HCM. The SGLT2i dapagliflozin was recently shown to reduce the incidence of cardiovascular death and the progression of HF in nondiabetic patients with HF and

reduced ejection fraction.¹⁵⁶ Since the cardiometabolic effects of SGLT2i are independent of the presence of diabetes mellitus, it is likely that these drugs could also benefit patients with HCM who develop HF with reduced ejection fraction. Nevertheless, most patients with HCM develop symptoms of HF with preserved ejection fraction or LV outflow tract obstruction and data to support the use of SGLT2i in these patients are lacking. The results of a large cardiovascular outcome trial in patients with HF and preserved ejection fraction are therefore eagerly awaited.¹⁵⁷

Targeting Metabolism in HCM

Metabolic therapy with compounds that inhibit mitochondrial fatty acid oxidation (eg, trimetazidine and perhexiline) may be effective as general treatment of HCM.^{137,138,158,159} These drugs are thought to improve ATP regeneration by shifting mitochondrial metabolism away from fatty acid oxidation to more oxygen-efficient glucose oxidation.¹⁵⁸ This might be particularly beneficial during the early phase of disease development, since established HF is characterized by a major increase in anaerobic glycolysis. An ongoing clinical trial testing the effect of trimetazidine on myocardial efficiency in phenotype-negative *MYH7* mutation carriers will yield more insight herein.¹³⁸ Boosting mitochondrial ATP production may aid the myocardium in coping with the increase in workload caused by primary mutation-induced myofilament defects and increased preload and afterload in the context of obesity. However, in patients with HCM with defective myocardial insulin signaling, such drugs may be ineffective because of impaired myocardial glucose uptake. In addition, inhibition of fatty acid oxidation without lowering circulating levels and myocardial uptake of fatty acids may make the heart subject to lipotoxicity,^{160,161} possibly mitigating the positive effects of improved glucose oxidation. Reducing fatty acid uptake and oxidation may be achieved via inhibition of fatty acid translocase,¹⁶² which has recently been demonstrated to hold therapeutic potential in the treatment of diabetic cardiomyopathy.¹⁶³ This strategy may therefore also be a future therapeutic target for HCM treatment, particularly in patients with coexisting DM-II.

CONCLUSIONS

Obesity is associated with increased HCM penetrance and is characterized in patients by a more severe phenotype and worse disease progression. Obesity and its associated comorbidities affect the myocardium, harboring sarcomere mutations via multiple mechanisms. These include neurohumoral activation, hemodynamic changes, LV remodeling, inflammation, perfusion defects, and metabolic

perturbations, which may both sensitize mutation-induced defects and impair cardiac function independently. Gaining more insight in the interplay between obesity- and mutation-induced defects in HCM development and progression requires extensive (pre) clinical study. Clinically, we highlight body weight loss and control as a key component of patient management. Novel antidiabetic drugs and metabolic therapy aimed at improving glucose metabolism may be effective pharmacological treatment strategies in obese patients with HCM.

ARTICLE INFORMATION

Affiliations

From the Department of Physiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands (E.E.N., D.W.K., J.v.d.V.); Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands (B.D.W., R.A.d.B.); and Netherlands Heart Institute, Utrecht, The Netherlands (J.v.d.V.).

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Disclosures

None.

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