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Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy

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IMPACT OF OBESITY
ON THE PHENOTYPE AND CLINICAL COURSE
OF HYPERTROPHIC CARDIOMYOPATHY

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Iacopo Olivotto MD[1], Barry J. Maron MD[2], Benedetta Tomberli MD[1], Evan Appelbaum MD[3,4],

Carol Salton[3,4], Tammy S. Haas RN[2], C Michael Gibson MD[3,4], Stefano Nistri MD[1],

Eleonora Servettini MD [1], Raymond H. Chan[4], MD James E. Udelson MD[5], John R. Lesser MD[2],

Franco Cecchi[1], Warren J. Manning MD[3,4] and Martin S. Maron MD[5]

Referral Center for Myocardial Diseases, Azienda Ospedaliera Universitaria Careggi, Florence Italy; [2]Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; [3]Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Hospital and Harvard Medical School, Boston, Massachusetts; [4]PERFUSE Core Laboratory and Data Coordinating Center, Harvard Medical School, Boston, Massachusetts; [5]Division of Cardiology, Tufts Medical Center, Boston, Massachusetts.

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Address for correspondence: Dr. Iacopo Olivotto, MD
Dipartimento Cuore e Vasi
Azienda Ospedaliera Universitaria Careggi
Viale Pieraccini 19, 50134 Firenze, Italy
Tel/Fax: 39 055 7949335
Email: olivottoi@aou-careggi.toscana.it

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ABSTRACT

Background. It is unresolved whether clinical variables promoting left ventricular (LV) hypertrophy in the general population, such as obesity, may influence cardiac phenotypic and clinical course in patients with hypertrophic cardiomyopathy (HCM). Therefore, we assessed the impact of body mass index (BMI) on disease expression in a large HCM cohort. Methods. In 275 adult HCM patients (age 48±14 years; 70% male), we assessed the relation of BMI to LV mass (determined by cardiovascular magnetic resonance [CMR] and heart failure progression. Results. At multivariate analysis, BMI proved an independent predictor of the magnitude of hypertrophy: pre-obese and obese HCM patients (BMI 25-30 and >30 kg/m^2, respectively) showed a 65% and 310% increased likelihood of an LV mass in the highest quartile (>120 g/m^2), compared to normal weight patients (BMI <25; hazard ratio [HR] 1.65, 95%CI 0.73-3.74; p=0.22 and 3.1, 95%CI 1.42-6.86;p=0.004, respectively). Other predictors of LV mass >120 g/m^2 were LV outflow obstruction (HR 4.9; 95%CI 2.4-9.8; p<0.001), systemic hypertension (HR 2.2; 95%CI 1.1-4.5; p=0.026) and male gender (HR 2.1; 95%CI 0.9-4.7; p=0.083). Over a 4.7±2.3 year follow-up, obese patients showed a 3.6 HR (95%CI 1.2-10.7; p=0.02) for developing NYHA class III symptoms compared to non-obese patients, independent of outflow obstruction. Of 31 patients in NYHA class III at final evaluation, 4 (13%) were normal weight, 7 (23%) were pre-obese and 20 (65%) were obese (p=0.037). Conclusions. In HCM patients, extrinsic factors such as obesity can independently impact phenotypic expression and LV mass, as well as dictate the progression of heart failure symptoms.

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Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, characterized by heterogeneous phenotypic expression with extreme diversity in the pattern and extent of left ventricular hypertrophy (LVH), due to molecular pathways and triggers that remain largely unexplained (1-5). In the majority of HCM patients, the disease is associated with mutations in genes encoding proteins of the cardiac sarcomere, most commonly beta-myosin heavy chain and myosin-binding protein C (1-3). While these molecular defects are considered responsible for the development of LVH, there is currently no conclusive evidence to explain the variability in phenotypic expression of HCM, ranging from massive degrees to absence of LVH even within the same family (1,4-6).

Among several hypotheses, the interplay of modifier genes and environmental factors has been commonly offered as a potential explanation for phenotypic diversity (7,8). To date however, the possibility of an environmental modulation of the HCM phenotype remains speculative, and even the impact of an obvious candidate variable, such as obesity, known to promote LVH in the general population, is unresolved (9-13).

In addition, it is unknown whether the adverse metabolic and hemodynamic effects of obesity, to which HCM patients may be exposed during the long-term course of their disease, ultimately affect symptomatic status and prognosis (14,15). Therefore, the present study was designed, in a large cohort studied with cardiac magnetic resonance (CMR), to assess the impact of body mass index (BMI) on the phenotype, as well as clinical course of HCM.

METHODS

<u>Study population</u>

The study cohort comprised 275 adult patients with HCM (age >18 years, mean 48±14 years, 70% male, maximum LV wall thickness 21±5 mm) consecutively referred for CMR at 3 participating referral centers in the U.S. and Italy: Minneapolis Heart Institute Foundation, Minneapolis, MN. (n=168); Tufts Medical Center, Boston, MA. (n=45), and Careggi University Hospital, Florence, Italy (n=62). Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, nondilated LV (maximal wall thickness ≥15 mm), in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident (1,3). We excluded significant atherosclerotic coronary artery disease (>50% stenosis in 1 major artery) by virtue of 2 specific clinical or CMR criteria: 1- no study patient experienced an acute coronary event associated with increased cardiac enzymes or Q waves on ECG and 2- in all patients with LGE distributed in a single coronary vascular territory, hemodynamically significant coronary artery disease was excluded by arteriography or computed tomography angiogram. Furthermore, patients with prior cardiac surgery (including septal myectomy), alcohol septal ablation, chronic renal failure and type I diabetes mellitus were excluded. The study protocol was approved by the respective Internal Review Boards or research ethics committees of each institution, and written inform consent was obtained from each subject.

<u>Definitions</u>

Body mass index (BMI) was calculated as weight/(height x height) and expressed in kg/m^2. Patients were classified as *Normal Weight* (BMI range <25 kg/m^2), *Pre-Obese* (25-30 kg/m^2) and *Obese* (>30 kg/m^2), according to existing guidelines (14). Type 2 diabetes was defined (and treated) according to standard guidelines (16).

Systemic hypertension, was diagnosed based on resting blood pressure values >140/90 mmHg on ≥3 different examinations and treated medically to optimize blood pressure control, as per standard

international guidelines (16). All patients with hypertension had a diagnosis of HCM based on 1 or more of the following criteria: 1) HCM-causing sarcomere gene mutation or family history of HCM; 2) onset of hypertension occurring years after the diagnosis of HCM; 3) maximum LV wall thickness exceeding that expected by hypertension alone (i.e. >20 mm); 4) presence of marked mitral leaflet elongation (17), 5) dynamic LV outflow obstruction (≥30 mmHg) under resting conditions (18); 6) distribution of late gadolinium enhancement (LGE) by contrast CMR consistent with HCM (i.e. preferentially mid-wall or transmural, and not confined to a single coronary vascular territory) (3,5,19).

Echocardiography

Echocardiographic studies were performed with commercially available instruments. LV hypertrophy was assessed with two-dimensional echocardiography, and the site and extent of maximal wall thickness were identified. Maximal end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the chamber. LV outflow obstruction, due to mitral valve systolic anterior motion and mitral-septal contact, was identified by a peak instantaneous outflow gradient ≥30 mm Hg occurring under basal conditions (n=57) (18). Two-hundred and eighteen patients were nonobstructive at rest, (basal gradient <30 mmHg), of whom 105 (age 43±13 years, 72% males) and underwent maximal symptom-limited exercise echocardiography, as previously described (18); 50 developed dynamic gradients ≥30 mmHg during effort or recovery (range 48-155 mmHg), and were considered to have provokable outflow obstruction.

Cardiovascular Magnetic Resonance (CMR)

All CMR examinations were performed using commercially available scanners (Philips ACS-NT 1.5T Gyroscan-Intera, Best, Netherlands) and a commercial cardiac coil. Electrocardiographic gated, steady-state, free precession breath- hold cines in sequential 10 mm short-axis slices (no gap) were acquired starting parallel to the atrioventricular ring and covering the entire ventricle. LV end-diastolic and end-systolic volumes, LV mass and wall thickness were calculated with commercially available work-stations (View Forum, Philips Medical System, Netherlands) (17,19).

For calculation of LV mass, the endocardial and epicardial borders of the LV were manually planimetered on successive short-axis cine images at end-diastole. The most basal slice at end-diastole was visually inspected and, if ventricular myocardium was present, it was planimetered and included in the mass calculation. If myocardium but no intracavitary blood pool was present on the most apical slice, it was included in the mass calculation by planimetering only the epicardial border. Particular care was taken to avoid including papillary muscles in the LV mass calculation. LV mass was derived by the summation of discs method and multiplying myocardial muscle volume by 1.05 g/cm^3 (19). LV mass was indexed to body surface area (BSA). Maximum end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the LV wall. CMR measurements were performed by an experienced investigator at each center, blinded to the results of echocardiography. The presence of LGE was assessed by visual inspection 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering; Berlin, Germany) with breath-held segmented inversion-recovery sequence (inversion time 240 to 300 ms) which was acquired in the same views as the cine images (19).

Statistical Methods

Data were expressed as mean±SD. For the comparison of two and more than two normally distributed variables, we employed Student's t-test and one-way ANOVA followed by Bonferroni's post-hoc test, respectively. Chi-square test was utilized to compare non-continuous variables expressed as proportions; however, Fisher's exact test was employed when one or more cells in the comparison table had an expected frequency of less than 5. Independent predictors of increased LV mass index were assessed by stepwise (forward conditional) multivariate logistic regression analysis. Survival was assessed by Cox proportional hazard regression. The survival curve was constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. P-values are two-sided and considered significant when <0.05. Calculations were performed with SPSS 12.0 software (Chicago, IL).

RESULTS

<u>Prevalence of obesity</u>

The 275 HCM patients had an average BMI of 29.1±6.1 kg/m^2, ranging from 16.2 to 49.3 kg/m^2. Sixty-nine patients (25%) were in the normal weight range (BMI<25; average 22.3±2.1), 105 (38%) were pre-obese (BMI 25-30; average 27.4±1.4), and 101 (37%) were obese (BMI>30; average 35.4±4.8) (Table 1). Overall, 107 patients (39%) were found to have LV outflow obstruction (i.e. a peak instantaneous outflow gradient ≥30 mmHg) occurring either under basal conditions (n=57) or during physiologic exercise (n=50). Seventy-five patients (27%) had a history of controlled systemic hypertension and 14 (5%) had adult-onset, type II diabetes. LV outflow obstruction, both under resting conditions and elicited by exercise, was disproportionally prevalent in pre-obese and obese patients (Figure 1, Table 1). Likewise, systemic hypertension and diabetes were more prevalent in pre-obese and obese compared to normal weight patients (Table 1); 38 of the 101 obese HCM patients (38%) were also hypertensive.

<u>Relation of BMI to LV mass, volume and function</u>

Average LV mass index in the HCM patient cohort was 104±40 g/m^2, ranging from 41 to 329 g/m^2 (highest quartile cut-off 120 g/m^2), greater in males (109±41 g/m^2 vs. 91±36 in females, p<0.001), (Table 2). Compared to normal weight patients, LV mass index progressively increased in pre-obese and obese patients: 95±46, 100±31 and 114±43 g/m^2, respectively (overall p=0.005; obese patients p<0.05 vs. each other group)(Figure 2), reflecting a direct relationship between LV mass and BMI (correlation coefficient=0.23; p<0.001). Conversely, maximum LV wall thickness was virtually identical in normal weight, pre-obese and obese patients (22±6 mm, 21±5 mm and 21±5 mm, respectively; p=0.27).

Increased LV mass with respect to body weight was associated with higher LV end-diastolic volume index: 66±14 ml/m^2 in normal weight, 77±18 ml/m^2 in pre-obese and 83±20 ml/m^2 in obese patients (overall p<0.001) (Figures 3 and 4). Nevertheless, average LV end-diastolic dimension remained within the normal range for each group (i.e., nondilated LV cavity) (Table 2). Notably, when the subset of 168 nonobstructive

HCM patients was analyzed separately, the direct correlation of BMI and LV mass index persisted (correlation coefficient 0.22,p=0.004).

Conversely, LV systolic function, as expressed by ejection fraction (EF), did not differ among the 3 BMI classes (p=0.86); by virtue of greater end-diastolic volumes, stroke volume index increased from normal weight to pre-obese to obese HCM patients, whereas mass/volume ratio was unchanged (Table 2). Prevalence of LGE was increased in pre-obese and obese HCM patients (48% and 55%, respectively) compared to the normal weight patients (28%, overall p=0.001). However, average %LV mass occupied by LGE in individual patients did not differ between the subgroups (overall p=0.43) (Table 2).

Systemic hypertension was associated with increased LV mass index in our HCM cohort (118±44 g/m^2 vs. 98±36 in normotensive; p<0.001), although type 2 diabetes was not (LV mass index 104±41 g/m^2 vs. 104±21 in non-diabetic patients; p=0.98). Patients who were both obese and hypertensive had LV mass index values of 126±44 g/m^2, compared to 93±42 g/m^2 in those patients who were neither obese nor hypertensive (p<0.001).

Predictors of LV mass

A multivariate regression model was constructed to identify variables independently associated with greater magnitude of LV hypertrophy, defined by a LV mass in the highest quartile for the overall cohort, or >120 g/m^2. The model included BMI, age, gender, resting or provokable LV outflow obstruction, systemic hypertension and type 2 diabetes. BMI proved an independent predictor of LV mass >120 g/m^2, with an hazard ratio (HR) per unit increase of 1.07 (95%CI 1.01-1.13; p=0.019).

Pre-obese HCM patients showed 65% increased likelihood of assignment to the highest LV mass index quartile, compared to normal weight patients (HR: 1.65; 95%CI: 0.73-3.74; p=0.22), while in obese patients this likelihood increased >300% (HR: 3.1; 95%CI: 1.42-6.86; p=0.004). Other variables associated with LV mass >120 g/m^2 were: resting or provokable outflow obstruction (HR: 4.9; 95%CI: 2.4-9.8; p<0.001), systemic hypertension (HR 2.2; 95%CI 1.1-4.5; p=0.026) and male gender (HR: 2.1; 95%CI 0.9-4.7; p=0.08).

Over a 4.7±2.3 year follow-up after CMR, there were 25 deaths (or equivalents), of which 6 were non-cardiac and 19 were HCM-related. Of the latter 19 death events, 12 were sudden (including 7 deaths, 2 patients resuscitated from cardiac arrest and 3 appropriate ICD discharges for ventricular tachycardia/fibrillation). In addition, there were 6 heart failure-related events (3 deaths and 3 heart transplants), and 1 postoperative death (surgical septal myectomy). There was no difference in all-cause mortality among the 3 BMI classes (Figure 5).

In the 256 patients who were alive at the end of follow-up, those with obesity were however almost 3-fold more likely to have developed progressive NYHA class III-IV symptoms at most recent evaluation, compared to normal weight patients (overall p=0.027) (Figure 5). Noticeably, of those 31 survivors in NYHA class III at the end of follow-up, 4 (13%) were normal weight, 7 (23%) were pre-obese and 20 (65%) were obese (p=0.037). Independent predictors of NYHA class III symptoms at end of follow-up were obesity (HR 3.6; 95%CI 1.2-10.7; p=0.02), female gender (HR 4.3; 95%CI 1.5-12.4; p=0.007) and LV outflow obstruction (HR 2.7; 95%CI 0.9-7.8; p=0.07); whereas age, history of atrial fibrillation and hypertension were not.

DISCUSSION

Obesity and the HCM phenotype

In HCM, the primary morphologic expression of LV hypertrophy has historically been considered solely a consequence of the gene mutation, with no evidence to date that environmental variables can influence phenotypic expression. (2,5,7,8). However, the extreme heterogeneity of phenotypic expression among HCM patients, even in family members sharing the same mutation (6), implies that other determinants of cardiac morphology must be operative (2,3-5). For example, greater LV mass has been observed in male patients and those with dynamic LV outflow obstruction (18), suggesting the disease

phenotype may be sensitive to environmental modulation (20). In order to address this issue, we have considered whether obesity, an established cardiovascular risk factor known to promote LVH in the general population, may influence the magnitude of LV mass and prognosis in a large HCM cohort.

Our data demonstrate that obesity is independently associated with increased LV mass, establishing a novel principle that environmental variables can influence disease expression in a primary genetic cardiomyopathy such as HCM (19), a concept also relevant to other cardiomyopathies (20). Indeed, BMI was a powerful predictor of severe LV mass increase in our HCM patients, independent of other important determinants such as gender and dynamic LV outflow obstruction (19), as well as systemic hypertension. Furthermore, obesity appeared to have an important role in determining the progression and severity of heart failure symptoms (5).

In our HCM patients, the relationship between BMI and LV mass became particularly evident for BMI values >30. Obese patients were >3 times as likely to have a marked increase in LV mass exceeding 120 g/m^2, compared to those of normal weight. This increase in LV mass was driven primarily by greater end-diastolic volume (which nevertheless remained within normal limits when indexed to body size). In the general population, LV remodeling associated with chamber enlargement is an established consequence of obesity, which normalizes stroke volume index in the presence of increased oxygen requirement, thereby reflecting a physiologic adaptation to body weight (12,13,15,21,22). This principle was also supported by our observation that greater LV cavity volume in obese HCM patients was accompanied by preserved systolic function, resulting in an increased stroke volume index (12,13,21,22).

Notably, absolute LV wall thickness was unaffected by body weight, with obese patients showing maximum thickness values virtually identical to those in patients of normal weight. This finding suggests that the 2 features which most differentiate HCM from secondary forms of LVH, i.e. the asymmetric distribution of LV thickening and the often marked degree of regional hypertrophy, are largely unaffected by environmental modulation (4,7). Therefore, neither the current clinical diagnostic criteria for HCM nor

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decision-making for primary prevention of sudden death with ICDs (both based on maximum absolute LV wall thickness) (1,3,23-25), require adjustment with respect to BMI in adult patients.

Obesity and symptomatic status/outcome

During an average follow-up of almost 5 years, obese HCM patients had a 3.6-fold increased risk of developing severe functional limitation (NYHA functional class III) compared to non-obese patients, independent of other known determinants of heart failure symptoms such as outflow obstruction and atrial fibrillation (26). It was, however, difficult to ascertain precisely what proportion of functional limitation was due directly to obesity, as opposed to the consequences of HCM disease state (1,3). Nevertheless, symptomatic obese patients showed no impairment in LV ejection fraction, indicating that their severe disease profile was not due to progressive systolic dysfunction (or "end-stage" HCM) (5). In the general population, obesity is an important predictor of heart failure (14,15,27), associated with multiple and often profound changes in the cardiovascular system, including increased cardiac oxygen requirement, neurohormonal activation, increased oxidative stress, increased cardiac output and expanded central blood volume causing hemodynamic overload in the face of reduced cardiac efficiency (15,27). Likewise, our data suggest that excessive body weight in HCM patients may impact importantly on symptom progression, potentially triggering a cycle of event in which obesity leads to an obligatory sedentary lifestyle, further increases in BMI and, ultimately, worsening of heart failure symptoms (14). Whether significant weight loss will lead to reduction of symptoms and LV mass in obese HCM patients remains unresolved, although these data support future longitudinal studies aimed at clarifying this issue (30).

On the other hand, obesity itself did not confer an independent survival disadvantage during follow-up in our HCM cohort. This finding suggests that other variables are more relevant than body weight in determining the prognosis of this complex disease (3,5,26), and is consistent with the elusive relationship of body weight to outcome in cardiovascular disease at large (27,28). Indeed, while obesity is associated with increased morbidity and mortality in the general population (9,14,27), a high BMI represents a strong

independent predictor of favorable outcome in patients with chronic heart failure, a phenomenon known as the "obesity paradox" (28).

Significance of LV outflow obstruction and hypertension

LV outflow obstruction was >2-fold more prevalent in obese HCM patients compared to those of normal weight, and associated with further increase in LV mass (17-19). Although the mechanisms accounting for this relationship are uncertain, the abnormally increased adrenergic drive associated with obesity may predispose to development of intraventricular gradients (29). Such observation may suggest that excess LV hypertrophy in obese patients is principally mediated by outflow obstruction and afterload mismatch (19). Nevertheless, when the present analysis was restricted to nonobstructive HCM patients, the association between BMI and LV mass persisted, consistent with the concept that cardiac remodeling due to excess body weight is largely independent of (although synergistic to) outflow obstruction (12,19).

Systemic hypertension was another modifier of the HCM phenotype (9,11). As expected, the prevalence of elevated blood pressure increased with body weight, and was present in almost 40% of obese patients in our HCM cohort. Even though pharmacologically treated according to existing guidelines (16), hypertension doubled the likelihood of severe LV hypertrophy in these patients, independent of other determinants of LV mass. Furthermore, the combination of obesity and hypertension was associated with the highest LV mass values observed for any subset within the cohort. Thus, the present findings support the concept that the neurohormonal abnormalities associated with hypertension may impact LV mass in HCM patients (14,15,20,31), and thereby represent a relevant therapeutic target (15).

Conclusions

The present study provides evidence that obesity is an independent promoter of adverse cardiac remodeling associated with increased LV mass in patients with HCM. These observations underscore the novel principle that the primary phenotypic expression in this complex, heterogenous heart disease is also subject to environmental variables and not solely the product of disease-causing sarcomere mutations. In addition, obesity appears to play a role in the development and progression of heart failure symptoms in

HCM, supporting the need for follow-up studies clarifying whether modulating obesity can improve clinical course.

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FIGURE LEGENDS

Figure 1. Prevalence of LV outflow obstruction in relation to BMI. Bar graph illustrating the proportion of patients in each BMI class with LV outflow tract obstruction (≥30 mmHg) at rest or with exercise. Increase in BMI is associated with greater likelihood of an obstructive pathophysiology. Symbols: *= p<0.05 vs. Normal Weight; §= p<0.05 vs. Pre-Obese.

Figure 2. Impact of BMI on LV mass. Each panel shows mean (±95% confidence interval for mean) for unadjusted LV mass and LV mass index in each of the 3 BMI classes. Overall P value for HCM patients was 0.005 (obese patients p<0.05 vs. each of the other 2 groups). Abbreviation: Wt = weight. Symbols: *=p<0.05 vs. Normal weight; †=p<0.05 vs. Pre-Obese.

Figure 3. Cardiac remodeling in an obese patient with HCM. Images from a 35-year old male patient with a BMI of 28 kg/m^2. LV mass was 367g (indexed 153 g/m^2), with a maximal wall thickness of 29 mm. LV end-diastolic volume was 235 ml (indexed 97 ml/m^2) and LV ejection fraction was 80%. **A**: CMR SSFP 4-chamber showing diffuse thickening with sparing of the apex. **B**: Corresponding Late gadolinium enhancement (LGE) imaging shows lack of fibrosis in LV. Asterisk (*) denotes subcutaneous fat, (+) denotes intrathoracic visceral fat.

Figure 4. Impact of BMI on LV volume and function. Panels show mean (±95% confidence interval for mean) LV end-diastolic volume index, LV ejection fraction and stroke volume index for the 3 BMI classes. Overall P values for each variable are provided in Table 1. Abbreviation: Wt = weight. Symbols: *=p<0.05 vs. Normal weight; †= p<0.05 vs. Pre-Obese.

Figure 5. Impact of BMI on survival. **Top.** Cumulative risk of all-cause mortality in normal weight, pre-obese and obese patients during follow-up. **Bottom.** Prevalence of HCM-related mortality and severe heart failure symptoms (NYHA functional classes 3 or 4) among survivors at the end of follow-up period. Abbreviation: Wt = weight. Symbol: * = p=0.03 vs other 2 groups.

Table 1. Clinical and Echocardiographic Features of the 275 HCM Patients in relation to BMI.

		Body Mass Index (Kg/m^2)			
	Overall	**Normal**	**Pre-Obese**	**Obese**	**P Value**
		BMI <25	**BMI 25-30**	**BMI >30**	
No. of Patients n (%)	**275**	**69** (25%)	**105** (38%)	**101** (37%)	
Male	192 (70%)	32 (46%)	81 (77%)	79 (78%)	<0.001
Age at diagnosis (y)	43±14	41±15	45±13	44±13	0.257
Age at CMR (y)	48±14	46±14	50±14	49±13	0.123
Body surface area (m^2)	1.97±0.25	1.73±0.18	1.99±0.2$^\blacklozenge$	2.11±0.23§	<0.001
Body Mass Index (Kg/ m^2)	29.1±6.1	22.3±2.1	27.4±1.4$^\blacklozenge$	35.4±4.8§	<0.001
Height (m)	1.71±0.12	1.68±0.09	1.75±0.12§	1.68±0.14	<0.001
Weight (Kg)	85±19	63±9	84±11	101±16§	<0.001
NYHA FC at first evaluation					
I	149 (54%)	37 (54%)	64 (61%)	48 (47%)	Overall
II	67 (24%)	19 (27%)	22 (21%)	26 (26%)	0.183
III	15 (5%)	3 (4%)	3 (3%)	9 (9%)	
Syncope	57 (20%)	10 (14%)	26 (25%)	21 (21%)	0.263
Atrial Fibrillation	30 (11%)	4 (6%)	12 (11%)	14 (14%)	0.248
Hypertension	75 (27%)	8 (12%)	29 (28%)	38 (38%)$^\blacklozenge$	0.001
Type II Diabetes	14 (5%)		4 (4%)	10 (10%)	0.012
Hypercholesterolemia	84 (31%)	9 (13%)	40 (38%)	35 (35%)	0.001

Table 1 (continued)

	Overall	Body Mass Index (Kg/m^2)			P Value
		Normal	**Pre-Obese**	**Obese**	
		BMI <25	BMI 25-30	BMI >30	
Echocardiography					
Left atrial diameter (mm)	44±8	42±7	44±8	46±7[#]	0.032
LV end-diastolic diameter (mm)	45±6	43±6	45±6	46±6[#]	0.025
Maximum LV wall thickness (mm)	21±5	22±6	21±5	21±5	0.272
With LV outflow obstruction	107 (39%)	15 (22%)	41 (39%)	51 (50%)[#]	0.001
In resting conditions	57 (21%)	10 (14%)	21 (20%)	26 (26%)[#]	0.201
Exercise-induced*	50 (18%)	5 (7%)	20 (19%)[#]	25 (25%)[#]	0.014
Medical treatment					
Beta-blockers	151 (55%)	28 (40%)	62 (59%)	61 (60%)	0.427
Verapamil	52 (19%)	9 (13%)	22 (21%)	21 (21%)	0.578
Amiodarone	15 (5%)	4 (6%)	6 (6%)	5 (5%)	0.850
Disopyramide	10 (4%)	2 (3%)	4 (4%)	4 (4%)	0.613
Diuretics	29 (10%)	2 (3%)	9 (8%)	18 (18%)[#]	<0.001
ACE-Inhibitors/sartans	40 (14%)	4 (6%)	14 (13%)	22 (21%)[#]	<0.01
Warfarin	14 (5%)	0	5 (5%)	9 (9%)	0.155

Abbreviations: FC= functional class; LV = left ventricular; NYHA = New York Heart Association.

Symbols: *= only subjects without resting LV outflow obstruction were exercised; # =p<0.05 versus Normal (BMI <25).

Table 2. Cardiovascular Magnetic Imaging Findings in 275 HCM Patients with Respect to BMI.

| | Overall | Body Mass Index (Kg/m^2) | | | P-Value |
| | | Normal | Pre-Obese | Obese | |
		BMI <25	BMI 25-30	BMI >30	
No. of Patients n (%)	**275**	**69** (25%)	**105** (38%)	**101** (37%)	
LV end-diastolic volume (ml)	151±45	115±29	154±38$^{\#}$	174±45*	<0.001
LV end-diastolic volume index (ml/m^2)	77±19	66±14	77±18$^{\#}$	83±20$^{\#}$	<0.001
LV end-systolic volume (ml)	43±22	33±17	44±23$^{\#}$	49±25$^{\#}$	<0.001
LV end-systolic volume index (ml/m^2)	22±11	19±9	22±13	23±11$^{\#}$	0.049
LV ejection fraction (%)	72±10	71±11	72±10	72±9	0.864
Stroke volume (ml)	108±33	82±23	109±28$^{\#}$	125±34*	<0.001
Stroke volume index (ml/m^2)	58±13	52±11*	57±12$^{\#}$	61±15$^{\#}$	0.002
LV mass (g)	205±85	165±84	198±61	240±94*	<0.001
LV mass index (g/m^2)	104±40	95±46	100±31	114±43*	0.005
Mass volume ratio	1.3±0.5	1.3±0.5	1.3±0.4	1.4±0.5	0.428
Patients with LGE	125 (46%)	19 (28%)	50 (48%)$^{\#}$	55 (55%)$^{\#}$	0.001
LGE mass (g)	22±23	29±25	23±25	18±21	0.432
LGE percent of LV volume (%)	6±9	10±14	7±9	5±6	0.088

Abbreviations: BMI=body mass index; LGE=late gadolinium enhancement; LV = left ventricular; NYHA = New York Heart Association.
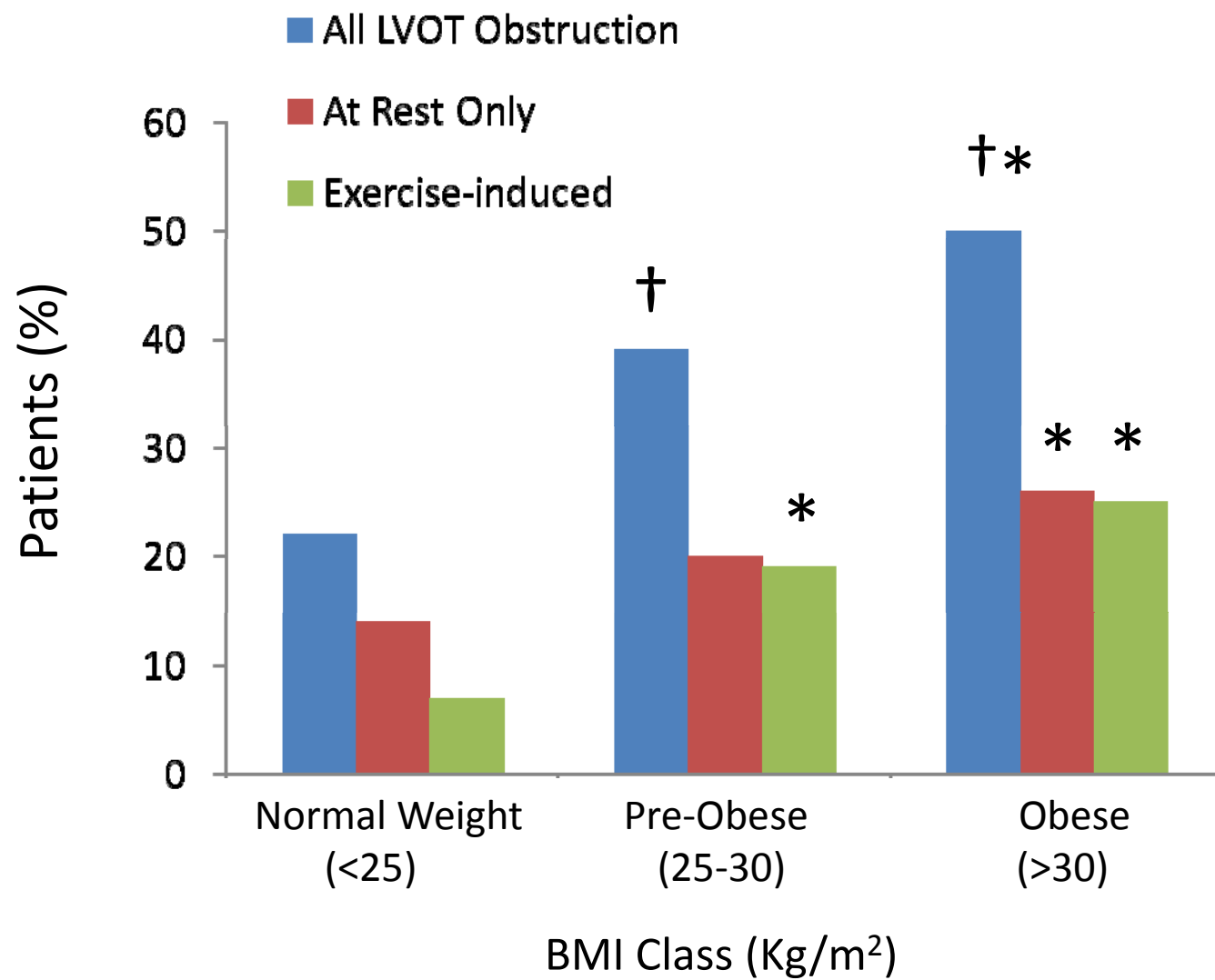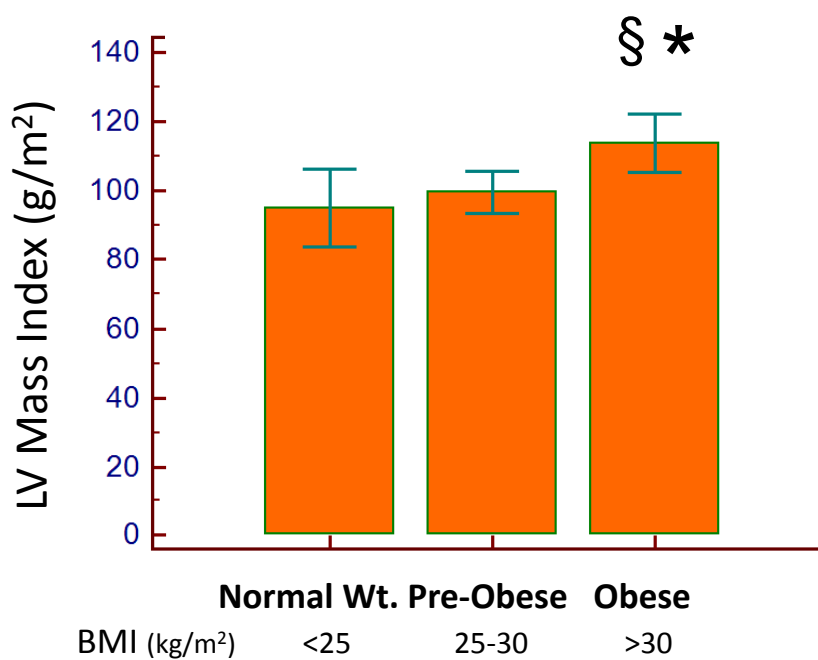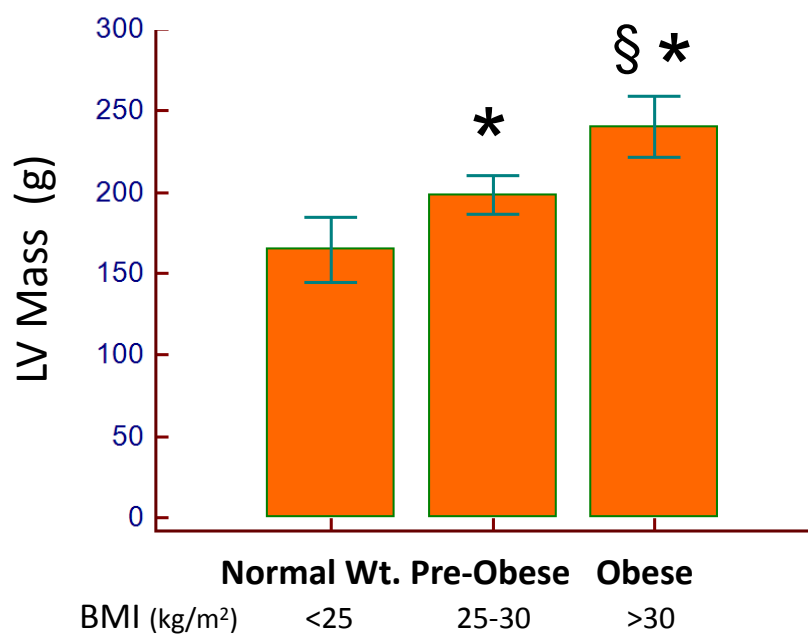
Symbols: * = p<0.05 versus the other 2 groups, # = p<0.05 versus Normal.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5