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Early LV remodelling patterns in overweight and obesity: Feasibility of cardiac CT to detect early geometric left ventricular changes

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ABSTRACT

Background: Obesity is an in independent risk factor for cardiovascular disease.
Goal: To describe the early LV remodelling pattern in patients with overweight and obesity and structurally normal hearts.
Methods: Consecutive patients (n = 2374), with structurally normal hearts and BMI ≥ 18.5 kg/m^2, undergoing prospective mid-diastolic ECG gated CTCA were selected. Left ventricular mass (LVM) and Left ventricular mid-diastolic volume (LVMDV) were measured. The concentricity index (LVM/LVMDV) were calculated. According to the definitions of the World Health Organization (WHO), the patients were divided into weight categories.
Results: The mean LVM ± Std. deviation in the subgroups according to WHO classification was 101.68 ± 28.99 g (normal weight), 115.79 ± 29.14 g (overweight), 123.8 ± 33.44 g (class I obesity), 125.85 ± 32.89 g (class II obesity) and 132.45 ± 37.85 g (class III obesity). ($p < 0.001$)

The mean LVMDV progressed with increasing WHO weight category from 112.37 ± 36.46 in patients with normal BMI to 140.26 ± 43.78 in patients with class III obesity. ($p < 0.001$)

The concentricity index was 0.935 ± 0.216 g/ml in patients with normal BMI, 0.979 ± 0.253 g/ml, 1.058 ± 0.635 g/ml, 0.996 ± 0.284 g/ml and 0.9768 ± 0.244 g/ml in patients with BMI categories 25–29.99, 30–34.99, 35–39.99 and ≥40 kg/m^2, respectively.
Conclusions: Our study demonstrates a non-linear (inverse U-shape) relationship between increasing BMI class and concentricity index, reaching its maximum at a BMI of 30–34.99 kg/m^2. Further increase in BMI results in LV dilation.

Introduction

Overweight and obesity are an increasing global health problem. In 2008, the worldwide prevalence of overweight and/or obesity was estimated at 1.4 billion persons. Approximately one third of whom were in the obese category [1]. Obesity is an independent risk factor for cardiovascular disease and is associated with type II diabetes mellitus, hypertension, coronary artery disease and heart failure [2]. Heart failure etiology in obesity remains ill defined. Left ventricular (LV) adaptation occurs and may be multifactorial in origin secondary to hypertension, increased exertion or high output state. Both LV dilation and LV concentric remodelling has been described in patients with obesity [3].

LVM mass is an independent predictor for adverse cardiac outcome [4]. Furthermore, the LV remodelling patterns also carry prognostic information [5,6].

Prospective mid-diastolic ECG gated cardiac CT is a validated tool to assess coronary artery disease. Compared to echocardiog-

Abbreviation: CCTA, cardiac computed tomography angiography; LV, Left ventricle; LVM, Left ventricular mass; LVMi, LVM indexed to body surface area; LVMDV, Left ventricular mid-diastolic volume; LVMDVi, LVMDV indexed to body surface area; DM type II, Diabetes mellitus type II; BMI, Body mass index.

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raphy and cardiac MRI, CT has the best spatial resolution. Contrast enhanced CT allows an accurate delineation of the myocardium from the ventricular blood pool. For these reasons, we postulated that this technique has the potential to detect early differences in left ventricular mass (LVM) and LV mid diastolic volumes (LVMDV) between persons with normal weight, overweight or obesity and a structurally normal heart.

Methods

Study population

This study population has been previously described in a research study aimed to establish normal reference values for LVM, LVMDV and LV wall thickness [7]. In summary, consecutive patients (n = 3234) referred for coronary CTA between November 2014 and November 2016 were enrolled into the University of Ottawa Heart Institute Cardiac CT Registry and were screened. Patients with known CAD (prior myocardial infarction or prior revascularisation), heart failure, congenital heart disease, heart transplant or prior cardiac surgery were excluded (587 patients).

To allow comparison between patients with normal weight and the subgroups with overweight and obesity, a new exclusion criterion was added to this dataset. 10 patients were excluded as being with underweight, defined by the WHO as subjects with a BMI < 18.5 kg/m^2 [8].

Subsequently 2374 patients, in whom a prospective mid-diastolic ECG triggered CTA was performed, were included in the final data set. The protocol was approved by the local research ethics board.

Coronary CTA image acquisition

The coronary CTA image acquisition protocol has been described elsewhere [7]. Briefly, patients without contraindications were pre-medicated with beta blockers targeting a heart rate of ≤ 65 beats/minute [9], and sublingual nitroglycerin (0.8 mg) before acquisition on a second-generation dual-source scanner (Somatom Definition Flash, Siemens, Forchheim, Germany, gantry rotation 280 msec, 64 × 2 x2 × 0.6 mm). Prospectively ECG triggered images were acquired in mid-diastole (100 msec acquisition centered around 70% of the R-R interval) at 80–120 kVp with an automated tube current (CARE dose 4D) [7]. A triphasic (100% contrast, 40%/60% contrast/saline,100% saline) intravenous administration protocol was used (Omnipaque 350 or Visipaque, GE Healthcare, Princeton, NJ, USA).

Measurements of the LV mass (LVM), left ventricular mid –diastolic volume (LVMDV) and LV wall thickness (WT_{LVMD})

Images were reconstructed with a slice thickness of 0.6 mm (increment of 0.4 mm) using i26f and i36f kernels and iterative reconstruction. Images were reconstructed in at least 3 phases (best diastolic phase and the outer bounds of the acquisition window) and images were post-processed which automatically detected the epicardial and endocardial borders. Contours were manually edited as needed. Papillary muscles were included in the blood volume measurement. The LVMDV and LV mass were calculated using the phase with the largest LV volume.

The 17 segment model was used and the measurements of the LV wall thickness were manually performed from corresponding reformatted short axis (SAX) views. The apical segment was excluded as no reliable SAX measurement can be made of this segment [10–12].

The LVM and LVMDV were indexed to the body surface area (BSA) [13]. The average LVmid-diastolic wall thickness (WT_{LVMD})) was assessed by summing the LVMDWT of the 16 LV wall segments divided by 16. The concentricity index was calculated as LVM/LVMDV.

Classification of the study participants according to weight class

To analyze the relationship between overweight/obesity and LV remodelling, the patient population was categorised in different weight categories, using the definitions of the WHO. All study participants were grouped: normal weight (BMI 18.5–29.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), class I obesity (BMI 30–34.9 kg/m^2), class II obesity (BMI 35–39.9 kg/m^2) and class III obesity (BMI ≥ 40 kg/m^2).

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as frequencies. Continuous variables were compared using Student's t-test, and statistical significance was defined as $p < 0.05$. For comparison between categorical variables, the pearson Chi-square test was used. Univariable and multivariable analyses were used with LVM, LVMDV and concentricity index as dependent variables. All analyses were performed in SPSS Version 25 (IBM, Armonk, NY, USA).

Results

Demographics of the study population

A total of 2374 patients were eligible for analyses (mean age = 57.6 ± 10.7 years, female 45.9%) (Table 1). When the patients were categorised according to their weight category, the distribution was as follows: 484 patients (20.4%) normal weight (BMI 18.5–29.9 kg/m^2), 944 patients (39.8%) with overweight (BMI 25–29.9 kg/m^2), 592 patients (25.9%) with class I obesity (BMI 30–34.9 kg/m^2), 222 patients (9.3%) class II obesity (BMI 35–39.9 kg/m^2) and 132 patients (5.6%) class III obesity (BMI ≥ 40 kg/m^2).

In the study population, type 2 diabetes, hypertension and dyslipidemia were present in 344 (14.4%), 1121 (47.2%) and 1172 (49.4%) of patients, respectively. When the patients were subdivided in normal weight, overweight and obesity, the prevalence of type 2 diabetes was 6%, 10.7% and 22% respectively and hypertension was present in respectively 33.3%, 43.1% and 58.5% of the cases. Table 1 summarizes the patient characteristics, including age, gender, weight, height, BMI, cardiovascular risk factors, and prevalence of peripheral vascular disease.

LV. remodelling parameters

The mean LVM ± Std. deviation in the subgroups according to WHO classification was 101.68 ± 28.99 g (normal weight), 115.79 ± 29.14 g (overweight), 123.8 ± 33.44 g (class I obesity), 125.85 ± 32.89 g (class II obesity) and 132.45 ± 37.85 g (class III obesity). ($p < 0.001$ for all WHO categories compared to patients with normal BMI) (Table2). A progression in WT_{LVMD} was seen with increased BMI category, ranging from 6.54 ± 1.16 mm in patients with normal BMI to 8.18 ± 1.61 mm in patients with BMI ≥ 40 kg/m^2 ($p < 0.001$ for all WHO categories compared to patients with normal BMI) (Table 2 and Fig. 1a)

The mean LVMDV progressed with increasing WHO weight category ($p < 0.001$ for all WHO categories compared to patients with normal BMI). Table 2 summarizes the mean LVMDV for the different WHO weight categories.

Fig. 1B shows means of the concentricity index with 95% confidence intervals and p-values when the population was subdivided

Table 1
Patient characteristics.

Patient demographics							
	Normal weight (BMI 18.5–24.99 kg/m^2)	Overweight (BMI 25–29.99 kg/m^2)	Obesity (BMI ≥ 30 kg/m^2)	p-value*	p- value**		
	N = 484	N = 944	N = 944		Normal weight vs. Overw.	Normal weight vs. Obesity	Over-weight vs. Obesity
	Mean ± SD.	Mean ± SD.	Mean ± SD.				
Age	59.5 ± 11.72	58.3 ± 10.9	56 ± 10.39	<0.001	0.062	<0.001	<0.001
Weight	65.3 ± 9.34	81.0 ± 10.22	100.6 ± 16.91	<0.001	<0.001	<0.001	<0.001
Height	168.4 ± 10.43	171.5 ± 9.99	169.4 ± 10.67	<0.001	<0.001	0.221	<0.001
BMI	22.8 ± 1.57	27.4 6 ± 1.45	35 ± 4.77	<0.001	<0.001	<0.001	<0.001
	n (%)	n (%)	n (%)				
Female	285 (59.8)	357 (37.8)	448 (47.4)	<0.001	<0.001	<0.001	<0.001
Vasc. risk fact.	n (%)	n (%)	n (%)				
PVD	51 (10.6)	72 (7.6)	109 (11.5)	0.026	0.064	0.576	0.04
Fam. History	217 (44.8)	462 (48.9)	508 (53.7)	0.014	0.141	0.002	0.038
Dyslipidemia	191 (39.5)	483 (51.2)	498 (52.6)	<0.001	<0.001	<0.001	0.52
Diabetes type II	29 (6.0)	101 (10.7)	214 (22.6)	<0.001	0..03	<0.001	<0.001
Smoking	213 (44.0)	415 (44.0)	462 (48.7)	0.112	0.987	0.09	0.038
Hypertension	161 (33.3)	407 (43.1)	553 (58.5)	<0.001	<0.001	<0.001	<0.001
Medication	n (%)	n (%)	n (%)				
ASA	181 (34.7)	411 (43.5)	429 (45.3)	0.022	0.260	0.040	0.428
ACE-inhibitors	61 (12.6)	172 (18.2)	229 (24.2)	<0.001	0.007	<0.001	0.001
ARB blockers	32 (6.6)	82 (8.7)	124 (13.1)	<0.001	0.171	<0.001	0.002
Beta blockers	139 (28.7)	308 (32.6)	338 (35.7)	0.037	0.132	0.008	0.155
Calcium blockers	56 (11.6)	120 (12.7)	179 (18.9)	<0.001	0.534	<0.001	<0.001
Diuretics	39 (8.1)	121 (12.8)	187 (18.7)	<0.001	0.007	<0.001	<0.001
Statins	148 (30.6)	395 (41.8)	421 (44.5)	<0.001	<0.001	<0.001	0.243
Metformin	25 (5.5)	79 (8.4)	177 (18.7)	<0.001	0.270	<0.001	<0.001
Other hypoglyc.	8 (1.7}	33 (3.5)	86 (9.1)	<0.001	0.048	<0.001	<0.001
Insulin	9 (1.9)	26 (2.8)	38 (4.0)	0.073	0.301	0.03	0.129
Coumadin	8 (1.7)	21 (2.2)	35 (3.7)	0.064	0.468	0.032	0.059
Nitrates	6 (1.2)	18 (1.9)	17 (1.8)	0.27	0.353	0.428	0.860
Bronchodilators	42 (8.7)	80 (8.5)	124 (13.1)	<0.001	0.897	0.013	0.001

BMI = body mass index; Vasc. Risk. Fact. = vascular risk factors; PVD = Peripheral vascular disease; Fam. history = familial history; ACE-inhibitors = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker, ASA = acetylsalicylate.

* p values: to compare the subgroups, one-way ANOVA was used for continuous variables and the pearson Chi-square test for categorical variables.

** p value, using T test for continuous variables and the Chi-square test for categorical variables.

Table 2
LV remodelling parameters in the different weight categories.

Mean values for BMI and LV remodelling parameters						
	LVM (g)			LVMi (g/m^2)		
	Mean	St-Dev	p value*	Mean	St-Dev	p value*
BMI (18.5–24.9) Ref.	101.68	28.99	Ref.	57.81	13.49	Ref.
BMI (25–29.9)	115.79	29.14	<0.001	58.66	12.34	0.245
BMI (30–34.9)	123.8	33.44	<0.001	58.4	13.16	0.475
BMI (35–39.9)	125.85	32.89	<0.001	56.44	12.82	0.169
BMI ≥ 40	132.45	37.85	<0.001	55.36	12.65	0.052
	LVMDV (ml)			LVMDVi (ml/m^2)		
	Mean	St-Dev	p value*	Mean	St-Dev	p value*
BMI (18.5–24.9) Ref.	112.37	36.46	Ref.	63.98	18.2	Ref.
BMI (25–29.9)	123.15	39.51	<0.001	62.41	17.84	0.12
BMI (30–34.9)	125.98	37.81	<0.001	59.41	19.17	<0.001
BMI (35–39.9)	132.95	47.36	<0.001	59.65	19.27	0.05
BMI ≥ 40	140.26	43.78	<0.001	58.78	15.94	0.001
	Concentricity index (g/ml)			WT_{LVMD} (mm)		
	Mean	St-Dev	p value*	Mean	St-Dev	p value*
BMI (18.5–24.9) Ref.	0.935	0.216	Ref.	6.54	1.16	Ref.
BMI (25– 29.9)	0.979	0.253	0.001	7.19	1.18	<0.001
BMI (30–34.9)	1.058	0.635	<0.001	7.58	1.47	<0.001
BMI (35–39.9)	0.996	0.284	0.005	7.57	1.36	<0.001
BMI ≥ 40	0.9768	0.244	0.057	8.18	1.61	<0.001

BMI = body mass index, LVM = Left ventricular mass, LVMi = LVM indexed to body surface area (BSA), LVMDV = Left ventricular mid-diastolic volume, LVMDVi = LVMDV indexed to BSA, St-Dev = standard deviation, WT_{LVMD} = average left ventricular mid-diastolic wall thickness.

* p values: to compare the subgroups with reference group (Ref.) being the subjects with normal BMI.

in patients with normal BMI, overweight and obesity, confirming increasing concentricity index as the overall dominant early LV remodelling pattern in patients with overweight and obesity.

However, when the subdivision was made according normal BMI, overweight, class I obesity, class II obesity and class III obesity, the concentricity index showed an inverse U-shaped curve (Fig. 1C). In this scenario, the concentricity index was 0.935 ± 0.216 in patients with normal BMI, 0.979 ± 0.253, 1.058 ± 0.635, 0.996 ± 0.284 and 0.9768 ± 0.244 respectively for patients in BMI categories 25–29.99, 30–34.99, 35–39.99 and $\geq 40\ kg/m^2$. ($p \leq 0.005$ for all WHO groups compared to patients with normal BMI, with exception of the patients with BMI $\geq 40\ kg/m^2$: $p = 0.057$) (Table 2 and Fig. 1C).

Fig. 2 shows the plot with BMI on the X axis and LVM (g) and LVMDV (ml) on the Y axis. Initially, LVM has a steeper slope than LVMDV, resulting in an increased concentricity index. Around a BMI of $30\ kg/m^2$, the slope of LVMDV becomes the steepest one, indicat-

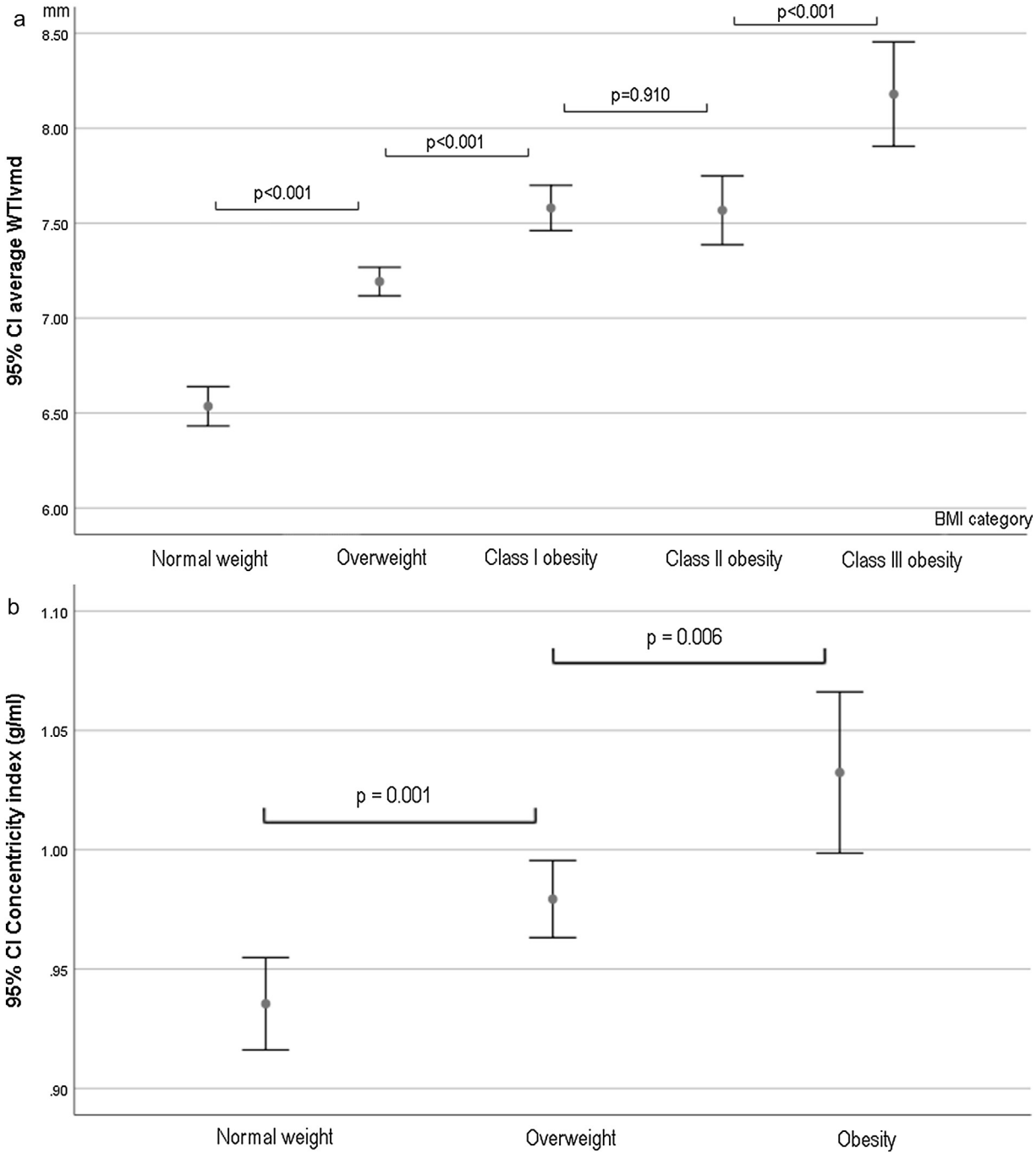

Fig. 1. Error plots with 95% confidence intervals.
Panel A demonstrates the increasing average LV mid-diastolic wall thickness (WT_{LVMD}) with increasing weight classes, using the WHO definitions.
Panel B confirms increasing LV concentricity with overweight and obesity.
Panel C demonstrates the course of the concentricity index (LVM/ LVMDV) with increasing WHO weight classes. Remark the inversed U-shape pattern. Concentricity goes up with increasing WHO weight categories to reach a maximum at obesity grade I (BMI 30–34.9 kg/m^2) with decrease of the concentricity if the BMI further increases.
Panel D demonstrate respectively similar patterns of the concentricity throughout the increasing WHO weight categories when the study population is subdivided in normotensive and hypertensive subjects (4A), in patients older or younger than 65 year and divided according to gender.

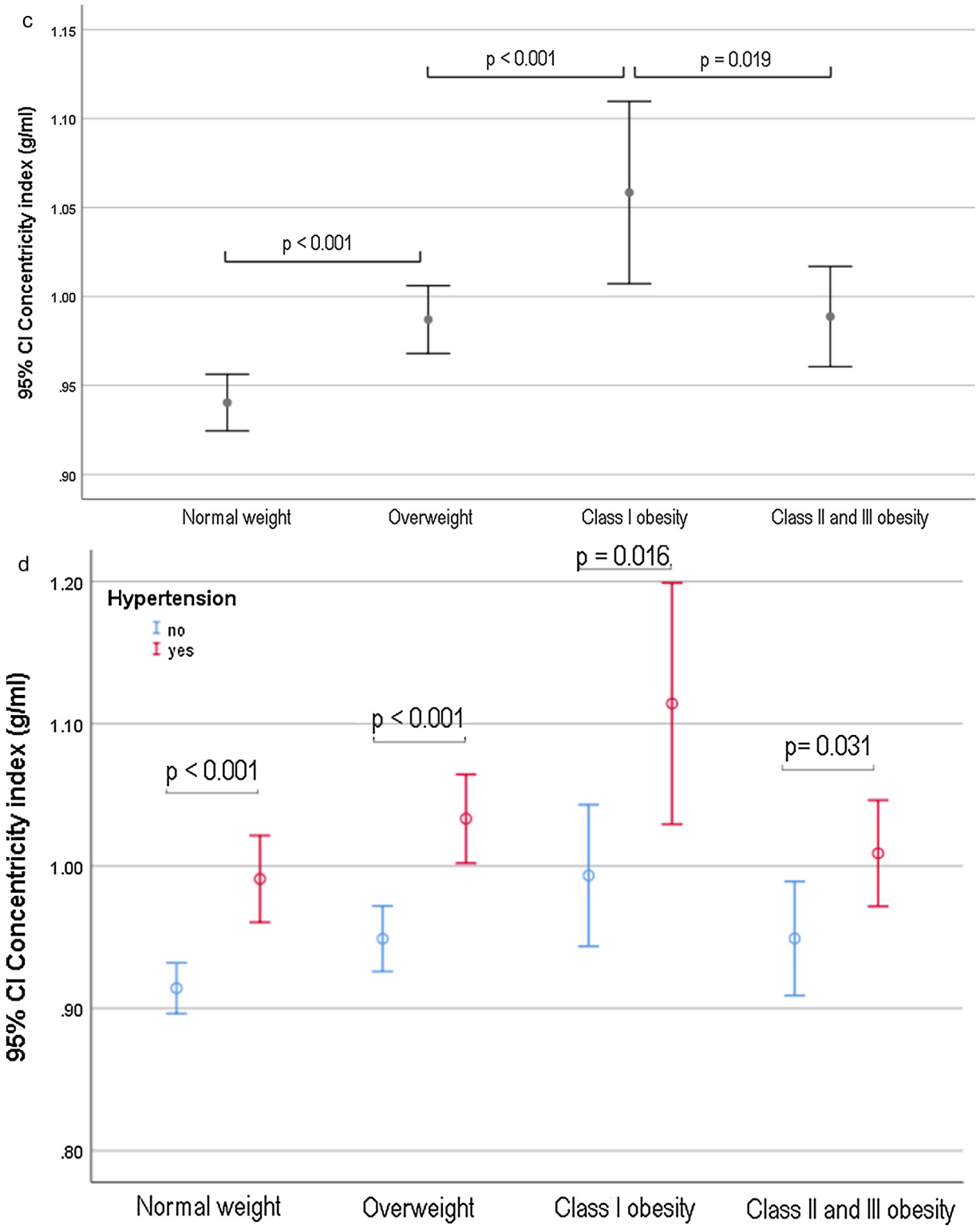

Fig. 1. (*Continued*)

ing that eccentric remodelling takes the overhand and concentricity (LVM/LVMDV) decreases.

When study population was divided in normotensive and hypertensive patients, the concentricity index showed a similar pattern throughout the different WHO weight categories as is demonstrated in Fig. 1D. Only the absolute mean value of LVM/LVMDV was higher in the patients with hypertension.

When the patients were divided into type II diabetes and non-diabetics, age <65 year and ≥65 year, and male versus female, the inversed U-shaped course of the concentricity index was preserved. (Fig. 1 Supplemental).

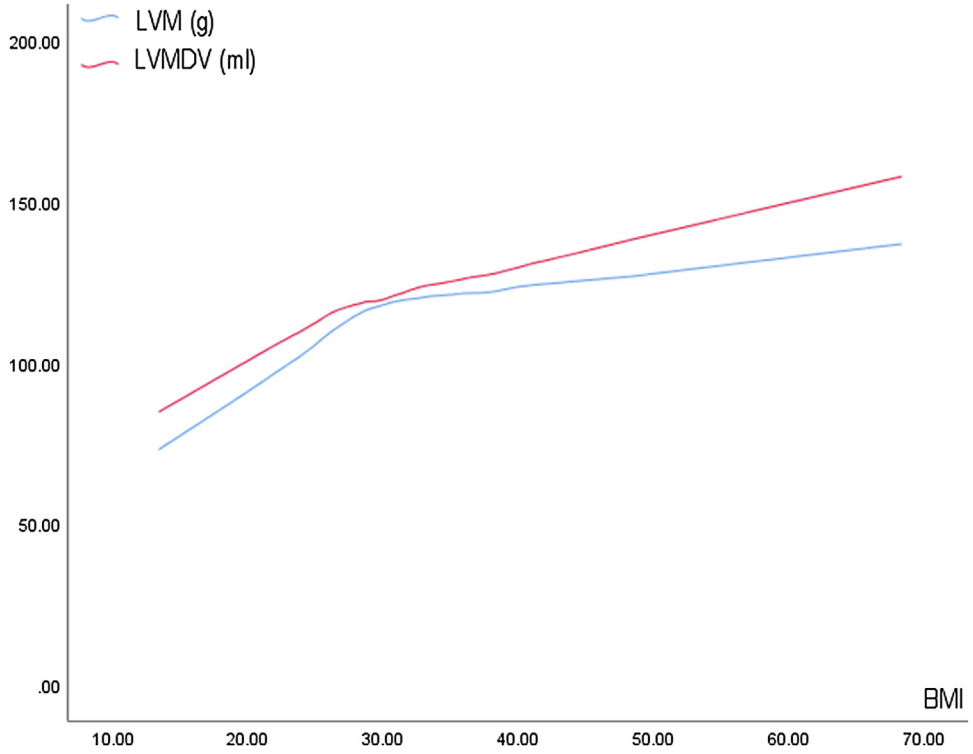

Fig. 2. The course of LV mass (LVM) and LV mid-diastolic volume (LVMDV) with increasing BMI. Remark initial steeper slope of LVM (blue line) compared to LVMDV (pink line). Around a BMI of 30 kg/m^2, the slope of LVMDV becomes the steepest one. This indicates that initially concentric remodelling is dominant, but in patient with obesity type II and morbid obesity, early eccentric remodelling progressively take the overhand (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Multivariable analyses

The results of the multivariable analyses with LVM, LVMDV and Concentricity index are listed in Table 3A, B and C, respectively. All independent variables with $p < 0.2$ in the univariable analysis were selected to build these multivariable models. In summary, the multivariable analyses show that type 2 diabetes is not an independent predictor for LVM. Hypertension is not independently associated with LVMDV. BMI is independently associated with LVM and LVMDV. However, the multivariable analysis failed to demonstrate a statically significant independent ($p = 0.082$) relation between BMI and concentricity index.

Discussion

This is the first study using prospective mid-diastolic gated cardiac CT to analyze early LV remodelling in patients with overweight or obesity. The study results confirm that early LV concentric remodelling is the dominant pattern in these patients. However, we demonstrate that the course of the concentricity index with increasing BMI has an inverse U shaped pattern.

Obesity is associated with hyperinsulinism, type 2diabetes mellitus, sleep apnea and an increased lifetime risk of heart failure [14]. A study with mean follow up of 14 years demonstrated an increase in risk of heart failure of 5% and 7% for respectively men and woman for each increment of BMI [15]. There is a doubling of the risk of heart failure of persons with obesity compared to people with a normal BMI [15].

Obesity induced LV remodelling has been extensively studied over the last decades. Nevertheless, there remains controversy. In the older medical literature, it was advocated that obesity would contribute to eccentric LVH, as a high output state to supply the excessive body mass was thought to result in larger ventricles

Table 3
Multivariable regression analyses exploring the relations between the LV remodelling parameters (LVM, LVMDV and Concentricity index) and clinical variables.

3A. Multivariable analysis: predictors of LVM

Variable	ß estimation		P value
Age	−0.363	0.051	<0.001
Gender	36.088	1.035	<0.001
DM type II	−2.120	1.535	0.167
Hypertension	6.744	1.103	<0.001
BMI	1.324	0.094	<0.001
Smoking	1.185	1.023	0.247
Dyslipidemia	−3.457	1.110	0.002

3B. Multivariable analysis: predictors of LVMDV

Variable	ß estimation		P value
Age	−0.739	0.073	<0.001
Gender	27.239	1.487	<0.001
DM type II	−6.807	2.205	<0.001
Hypertension	−0.435	1.585	0.654
BMI	1.190	0.135	<0.001
Smoking	−2.581	1.469	0.079
Dyslipidemia	−5.900	1.580	<0.001

3C. Multivariable analysis: predictors of concentricity (LVM/LVMDV)

Variable	ß estimation		P value
Age	0.003	0.001	<0.001
Gender	0.105	0.016	<0.001
DM type II	0.013	0.023	0.565
Hypertension	0.070	0.017	<0.001
BMI	0.002	0.001	0.082
Smoking	0.037	0.016	0.018
Dyslipidemia	0.025	0.017	0.143

BMI = body mass index, LVM = Left ventricular mass, LVMDV = Left ventricular mid-diastolic volume, DM type II = Type II diabetes mellitus.

in patients with obesity [16,17]. Recent studies systematically reported increased LVM and concentric remodelling in patients with obesity [18–21]. Abbasi et al. analysed 1151 participants from the MESA study [22]. LV geometric assessment was performed by CMR. Obese patients were found to have a higher VM/LV end-diastolic volume ratio compared to non-obese participants. An echocardiography study recruited 309 participants without prior treatment for hypertension [20]. This study showed that waist circumference was associated with concentric left ventricular hypertrophy and concentric remodelling, and not with end-diastolic diameter end eccentric hypertrophy. An echocardiography study included 51 young obese and otherwise healthy women. The study results demonstrated that obesity was associated with LV concentric remodelling in this subset of patients [18].

Our study differs from previous studies by its large sample size and the imaging modality to assess the LV remodelling. Our study results confirm a concentric remodelling as the dominant pattern in persons with overweight and obesity (Fig. 1B). However, our study adds to the current body of literature that the course of concentricity index with increasing BMI has an inverse U shaped pattern, reaching its maximum at the BMI class 30–34.9 kg/m^2 (Fig. 1C). Both LVM and LVMDV increase with increasing BMI. Initially, the LVM increases faster than the LVMDV, with subsequent increase of the concentricity index. At a BMI of 30 kg/m^2, there is a relative steeper increase in LVMDV than LVM resulting in eccentric LV remodelling, as was demonstrated in Fig. 2.

Noteworthy, in one of the pioneer autopsy series, studying cardiac remodelling in persons with over- weight and obesity, it was found that the heart weight proportionally increased with the excess in body weight to a threshold of 105 kg. Once this body weight was reached, increases in heart weight occurred to a lesser extent [23].

Alpert et al. addressed the issue why concentric remodelling may be reported more frequently than eccentrically remodelling. According to these authors, many studies reporting predominately concentric remodelling "have failed to adjust for or exclude patients with hypertension" [16]. It was hypothesized that in patients with obesity and normal cardiac output (CO) the stimulus for eccentric remodelling is absent and patients with obesity and normal CO and hypertension, concentric remodelling is facilitated.

However, our data don't support this hypothesis. The normotensive and hypertensive subgroups of patients showed a similar inverse U shaped pattern of the concentricity throughout the different BMI categories. Only, the absolute values of the concentricity were higher in the subgroup with hypertension (Fig. 1D).

When the patients were divided into type II diabetes and non-diabetics, age <65 year and ≥65 year, and male versus female, the inversed U-shaped course of the concentricity index was preserved. (Fig. 1 Supplemental) This sub-analysis suggests that these findings are consistent across different subpopulations.

LVM is an established risk factor for adverse cardiovascular outcome [4]. Several studies have demonstrated that LV remodelling patterns contain prognostic information [5,6,24,25]. It has been shown that a 4-tiered classification of LVH could differentiate the hazards for future adverse outcomes among these 4 classes in patients [26]. Eccentric LVH (concentricity normal, increased LVEDV) carries the worst prognosis [26]. As our study lacks outcome data, we cannot comment on the implications of the described U-shaped course of the LV concentricity index with increasing BMI. Nonetheless, if the assumption is made that the prognostic implications of LV remodelling patterns also apply for the early stages of LV early remodelling as in our study, our results suggest that the patients in highest BMI categories carry the most unfavorable early LV remodelling patterns.

As the concentricity index is a ratio (LVM/LVMDV), itś not subject of indexing to body habitus. Given the limitations and ongoing controversies on indexing to body surface area [27], LV concentricity looks an attractive concept, especially in obesity-related research and clinical applications.

The mechanisms of obesity causing LV remodelling as well as their relative contribution to the LV remodelling are only partially understood. Beside the earlier mentioned mechanical factors, more recent research has emphasized neurohormonal and metabolic alterations in obesity as the underlying processes promoting LV remodelling [3]. Insulin resistance and hyperinsulinism have been associated with increased levels of growth factor 1 which may contribute to myocardial hypertrophy [3,28]. Adipocytes produce angiotensinogen, angiotensin- I and angiotensin converting enzyme in addition to the systematically-produced components of the RAAS system. Angiotensin II is known to be a growth factor for the myocardium [29].

In addition, the hyperleptinemia status in patients with obesity may promote inflammation as well as myocardial hypertrophy via different pathways [30]. Low circulating levels of adiponectin, playing a key role in lipid and energy metabolism, in subjects with obesity may contribute to LVH, as adiponectin also inhibits myocyte hypertrophy [30]. Alterations in the autonomic nervous system in persons with have been proposed as a contributing factor to LVH [3].

Study limitations

Our study has 4 limitations that need to be discussed. First, its cross-sectional study design can be criticised. To determine a causal relation between BMI and cardiac remodelling, follow up of a cohort of patients over time would have been a better study design.

Secondly, it can be questioned if BMI is a too simplistic parameter to be used to search for a correlation between overweight-obesity and LV remodelling. A recent studies has been demonstrated that patients with subcutaneous adiposity and visceral adiposity (VQ) have slightly different LV remodelling patterns [19]. Nonetheless, BMI as a parameter to express overweight and obesity has been widely used as it is easy and low cost to obtain.

Third, overweight and obesity are associated with comorbidities, such as type 2 diabetes and hypertension. These comorbidities may have confounded the study results. However, it was thought that exclusion of patients with these comorbidities would no longer reflect the real world of obesity, as in our cohort of patients with obesity, 58.5% and 22.6% suffered from hypertension and type 2 diabetes, respectively. We tried to mitigate this limitation with the multivariable analyses suggesting that BMI is an independent predictor for LVM as well as LVMDV. Further, it was demonstrated that the course of concentricity with increasing BMI was similar for normotensive and hypertensive patients (Fig. 1D).

Finally, the goal of our study was to determine early trends in LV remodelling in individuals with overweight and obesity. Therefore, only patients with structurally normal hearts were included in our study. So, it can be argued that our study population only represents a subpopulation of persons with overweight and obesity.

Conclusion

Our study demonstrates that in a population with structural normal hearts, mid-diastolic prospective ECG gated cardiac CT already can readily depict the early related LV geometric changes in individuals classified as overweight or obese.

Consistent with recent research, our study demonstrated concentric remodelling is the dominant pattern in overweight/obesity. However, our study demonstrated a non linear relation relationship between increasing BMI class and concentricity. Initially, the

LV concentricity increases with increased BMI and reaches its maximum at a BMI of 30–34.9 kg/m^2. Further increases in BMI, results in progressive lowering of the concentricity, as eccentric remodelling becomes predominant.

Disclosures

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.orcp.2019.07.002.

References

[1] Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Prog Cardiovasc Dis 2014;56:426–33.
[2] Hubert H, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham heart study. Circulation 1983;67:968–77.
[3] Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and cardiac remodelling in adults: mechanisms and clinical implications. Prog Cardiovasc Dis 2018;61:114–23.
[4] Armstrong AC, Jacobs Jr DR, Gidding SS, Colangelo LA, Gjesdal O, Lewis CE, et al. Framingham score and LV mass predict events in young adults: CARDIA study. Int J Cardiol 2014;172:350–5.
[5] Huang BT, Peng Y, Liu W, Zhang C, Huang FY, Wang PJ, et al. Subclassification of left ventricular hypertrophy based on dilation stratifies coronary artery disease patients with distinct risk. Eur J Clin Invest 2014;44:893–901.
[6] Gaasch WH, Zile MR. Left ventricular structural remodelling in health and disease: with special emphasis on volume, mass, and geometry. J Am Coll Cardiol 2011;58:1733–40.
[7] Juneau D, Erthal F, Clarkin O, Alzahrani A, Alenazy A, Hossain A, et al. Mid-diastolic left ventricular volume and mass: normal values for coronary computed tomography angiography. J Cardiovasc Comput Tomogr 2017;11:135–40.
[8] World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva, Switzerland. World Heal Organ Tech Rep Ser 1995;854:1–452.
[9] Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee: endorsed by the North American society for cardiovascular imaging (NASCI). J Cardiovasc Comput Tomogr 2016;10:435–49.
[10] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of echocardiography, a branch of the European society of cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
[11] Cerqueira M, Weissman N, Dilsizian V, Jacobs A, Kaul S, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the american heart association. Circ J Am Heart Assoc 2002;105:539–42.
[12] Bicudo LS, Tsutsui JM, Shiozaki A, Rochitte CE, Arteaga E, Mady C, et al. Value of real time three-dimensional echocardiography in patients with hypertrophic cardiomyopathy: comparison with two-dimensional echocardiography and magnetic resonance imaging. Echocardiography 2008;25:717–26.
[13] Mosteller R. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
[14] Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 2002;10:97S–104S.
[15] Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.
[16] Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Curr Obes Rep 2016;5:424–34.
[17] Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American heart association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. Circulation 2006;113:898–918.
[18] Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, et al. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. J Am Coll Cardiol 2004;43:1399–404.
[19] Abbasi SA, Hundley WG, Bluemke DA, Jerosch-Herold M, Blankstein R, Petersen SE, et al. Visceral adiposity and left ventricular remodelling: the multi-ethnic study of atherosclerosis. Nutr Metab Cardiovasc Dis 2015;25:667–76.
[20] Woodiwiss AJ, Libhaber CD, Majane OH, Libhaber E, Maseko M, Norton GR. Obesity promotes left ventricular concentric rather than eccentric geometric remodelling and hypertrophy independent of blood pressure. Am J Hypertens 2008;21:1144–51.
[21] Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, et al. The impact of obesity on the left ventricle: the multi-ethnic study of atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266–74.
[22] Lin E, Alessio A. What are the basic concepts of temporal, contrast, and spatial resolution in cardiac CT? J Cardiovasc Comput Tomogr 2009;3:403–8.
[23] Smith H, Willius F. Adiposity of the heart. Arch Intern Med 1933;52:911–31.
[24] Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, et al. Adverse prognostic significance of concentric remodelling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol 1995;25:871–8.
[25] Verma A, Meris A, Skali H, Ghali JK, Arnold JM, Bourgoun M, et al. Prognostic implications of left ventricular mass and geometry following myocardial infarction: the VALIANT (VALsartan In Acute myocardial iNfarcTion) echocardiographic study. JACC Cardiovasc Imaging 2008;1:582–91.
[26] Khouri MG, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the Dallas heart study. Circ Cardiovasc Imaging 2010;3:164–71.
[27] Redlarski G, Palkowski A, Krawczuk M. Body surface area formulae: an alarming ambiguity. Sci Rep 2016;6:27966.
[28] Iacobellis G, Ribaudo MC, Zappaterreno A, Vecci E, Tiberti C, Di Mario U, et al. Relationship of insulin sensitivity and left ventricular mass in uncomplicated obesity. Obes Res 2003;11:518–24.
[29] Kalupahana NS, Moustaid-Moussa N. The renin-angiotensin system: a link between obesity, inflammation and insulin resistance. Obes Rev 2012;13:136–49.
[30] Hall ME, Harmancey R, Stec DE. Lean heart: role of leptin in cardiac hypertrophy and metabolism. World J Cardiol 2015;7:511–24.