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Original article

MORPHOLOGICAL AND FUNCTIONAL CHANGES OF THE LEFT ATRIUM IN OBESITY

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Abstract

Obesity-related atrial cardiomyopathy is a clinical entity characterized by a variety of functional and structural abnormalities in the atria's myocardium. This study aimed to investigate the morphological and functional alterations of the left atrium (LA) in overweight and obese subjects.

The study included 56 subjects aged 47+9.6 years, categorized into 4 groups according to their body mass index (BMI): group 1 - overweight (BMI 25-29.9 kg/m^2); group 2 - class I obesity (BMI 30-34.9 kg/m2); group 3 - class II obesity (BMI 35-39.9 kg/m^2) and group 4 - class III obesity (BMI >40 kg/m^2). All subjects underwent two-dimensional (2D) conventional echocardiography and speckle tracking myocardial deformation assessment. Left atrial enlargement (LAE) was registered in all four groups, with an average value of LA diameter 40.0±4.9 mm and LA volume (LAV) indexed to height (LAVh) 35.0 $\pm$7.8 ml. Global longitudinal strain (GLS%) and circumferential strain (GCS%) of LA were lower than reference normal values in all groups. LAV indexed to body surface area (LAVI) correlated with hip circumference (r=0.264; p=0.049), whereas LAVh correlated with waist and hip circumference (r=0.378; p=0.004). Linear regression analysis showed that hip circumference was a predictive factor for increasing LAVI (B=0.114; p=0.049; 95%CI 0.000-0.227) and LAVh (B=0.266; p =0.0001; 95%CI 0.129–0.403).

LAVh is a clinically useful echocardiographic parameter to assess LA size in obese population. A sensitive method for detecting subclinical functional alterations of LA is assessment of its speckle tracking longitudinal strain.

Keywords: obesity-related atrial cardiomyopathy, myocardial deformation, 2D speckle tracking

Introduction

The worldwide increase of obesity prevalence and its relation to cardiovascular diseases has generated scientific interest regarding the effects of obesity on the myocardium. The structure and function of the myocardium in obesity undergo remodelling, which is the fundamental cause of obesity-related cardiomyopathy. Expert consensus from several cardiology associations defines atrial cardiomyopathy (AC) as a combination of structural, contractile, and electrophysiological alterations of the atria that have the potential to cause clinically significant symptoms[1,2]. The volume and pressure load of the atria, impaired myocyte

function, fat accumulation in the pericardium, atrial interstitial fibrosis, inflammation, and myocardial lipidosis are major contributors to obesity-related AC[3-14].

Obesity is a risk factor for atrial fibrillation (AF)[15-19]. Left atrial enlargement (LAE), an echocardiographic marker of remodelling in obesity, is one of the pathophysiological factors contributing to AF [20-22]. Despite the available treatments, AF is still linked with considerable mortality [23-26] and it is anticipated that AF incidence will increase in tandem with obesity prevalence. Obesity affects LA function as well. In the initial stages of obesity, the LA's reservoir function is reduced, whereas its pump function declines in the later stages of obesity [27-29].

Studies in obese pediatric population demonstrated that myocardial alterations are prevalent even in the early stages of obesity[21,30]. However, there are optimistic evidences that weight loss may reverse cardiac abnormalities[31-36]. We present 56 obese patients in whom we assessed the size of the LA using a two-dimensional (2D) conventional echocardiography and we evaluated the function through myocardial deformation of the LA using the 2D Speckle tracking technique.

Material and methods

Study population

Echocardiographic evaluation underwent 56 obese patients aged 47.7±9.6, who fulfilled the following inclusion criteria for the study: age >18 years; a body mass index of >25 kg/m2; and a history of obesity for more than one year. Exclusion criteria in the selection were the presence of: kidney failure (creatinine clearance eGFR<60 ml/min), lung disease (asthma and/or chronic obstructive pulmonary disease), valvular heart disease, coronary artery disease (previously diagnosed with coronary angiography) and hemoglobinopathies.

After a clinical and metabolic examination at the University Clinic for Endocrinology, Diabetes, and Metabolic Disorders, subjects underwent transthoracic echocardiographic evaluation at the University Clinic for Cardiology in Skopje, North Macedonia.

Subject parameters including age, sex, height, and weight were assessed. Body mass index (BMI) was determined by dividing the weight in kilograms by height in meters squared. According to the World Health Organization's categorization, patients were classified into four groups: 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). In addition, anthropometric measures representing visceral obesity, such as waist circumference (high risk >102 cm in males and >88 cm in females) and waist-to-hip circumference ratio, were assessed in the patients. The diagnosis of arterial hypertension was established by measuring systolic blood pressure at 140 mm Hg or diastolic blood pressure at 90 mmHg on two occasions and by collecting data on antihypertensive drug use. A questionnaire was also provided to the patients to assess the presence of obesity-related disorders such as arterial hypertension, type 2 diabetes mellitus, polycystic ovarian syndrome, obstructive sleep apnea, coronary artery disease, peripheral artery disease, and osteoarthritis. All patients underwent a 12-channel electrocardiogram (ECG) to identify who was suitable for sinus rhythm echocardiography.

Echocardiography

Experienced operators performed transthoracic echocardiography using commercially available echocardiographs (GE, Vivid 7) in accordance with the current recommendations of the American Society of Echocardiography[38,39] and a standardized protocol. To limit interobserver variability, a single cardiologist analyzed all tracings. A special software was

used for offline analysis (EchoPAC PC 08: GE Healthcare). A speckle tracking software was used to evaluate the deformation in accordance with the relevant guidelines of the professional associations.

The maximum value for left atrial volume (LAV) was calculated using the area-length approach and the LA area in 4- and 2-chamber views, as well as the shortest of the two LA long axes measured in the apical 2- and 4-chamber views (ellipsoid model). Thereafter, LAV was indexed to BSA and height. Left atrial enlargement (LAE) was defined: 1. male >35.7 mL/m and female >33.7 mL/m; and LAV indexed to height (LAVh) according to established reference value. LA ejection fraction (LPEF%) was calculated in percentage as the difference between maximal and minimal LAV divided by maximal LAV and multiplied by 100. Using PW Doppler, both velocity in early diastole (E-wave) and velocity in late diastole (A-wave) of the transmitral flow were determined in an apical 4-cavity segment. The velocity of movement of the mitral annulus in a 4-cavity apical segment was measured using tissue Doppler in early diastole (e') and late diastole (a') (TDI). Measures were taken at the lateral and interventricular walls, and an average of both measurements was calculated. The ratio E/e', which represents the mean pressure in the left ventricle (LV) and the pressure of the LV filling, was determined as a derived index. Peak atrial longitudinal strain (PALS), measured at the end of the reservoir phase, and peak atrial contraction strain (PACS), measured just before the start of the active atrial contraction phase, were calculated by averaging the values observed in all accepted LA segments[40]. The median normal value for global PALS was ≥39% and for global PACS ≥16%[41-42].

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as a mean ± standard deviation (SD). The difference between groups was tested using Pearson's Chi-square test for categorical variables and two-tailed test for continuous variables. Assessment of correlation was done by using the Pearson's correlation analysis. Multiple linear and/or logistic regression analyses were done using clinical and echocardiographic characteristics to identify independent predictors of echocardiographic changes. All data analyses were performed by using SPSS, version 25.0 (IBM SPSS, Inc., Chicago, Illinois, USA), and $p \leq 0.05$ was considered as statistically significant.

Results

Our study included 56 subjects, aged 47+9.6 years, with a larger number of female subjects (Table 1). The investigated group's average body weight was 34.6 kg/m^2. The predominant subjects' risk factors for cardiovascular disease were hypertension, dyslipidemia, and diabetes. According to BMI, subjects were categorized into four groups. Subjects' distribution is shown in Table 2. There were 36 women among the total number of participants, with a higher average age, BMI, and hip circumference than men (Table 3). Table 4 displays the LA measurements in the four groups of subjects. According to the analysis, the mean values of the LA dimensions and the LAVh increased as the weight increased, while the LAVI did not. PALS values for the longitudinal deformation of the LA during the time when LA functions as a reservoir were below the reference normal values for all four groups of patients (Table 4). Regarding PACS, values were lower, particularly for classes 2 and 3 of obesity. Cross-comparison revealed that groups did not differ statistically substantially in terms of LA size and function. Table 5 shows the correlation analysis. Higher BMI was not linked with normalized volume for either body surface area or height but was statistically substantially associated with higher LA dimension and volume. Furthermore, higher BMI was significantly associated with increased LAEF (%). Greater waist circumference was statistically significantly correlated with greater LA dimension, LA

volume, and LAVh, but not with LAVI. Likewise, waist circumference correlated positively with the left ventricular ejection fraction (%), and it was the only variable that correlated with the left ventricular mass index (LVMi). Hip circumference correlated statistically with LA dimension, LA volume, LAVI, LAVh, and LAEF (%). Waist-to-hip ratio was shown to have a single significant relationship with LA dimension.

Table 1. Baseline characteristics of 56 subjects

Age at echo (y)	47.7 ± 9.6
Sex male (%)/ female (%)	20 (35.7)/36 (64.3)
BMI (kg/m^2)	34.6 ± 5.1
Waist circumference (cm)	113.2 ± 14.2
Hip circumference (cm)	120.4 ± 13.7
Waist/hip ratio (cm)	0.93 ± 0.07
Hypertension (%)	44.6
Dyslipidaemia (%)	39.3
Diabetes (%)	33.3

BMI-body mass index (kg/m^2)

Table 2. Percentage representation of obesity class

	Frequency	**Percentage**
Overweight	9	16.1
Class I obesity	26	46.4
Class II obesity	13	23.2
Class III obesity	8	14.3

Table 3. Baseline characteristics of 56 subjects divided by gender

	Male n=20	**Female n=36**
Age (years)	46.3 ± 8.4	48.5 ± 10.1
BMI (kg/m^2)	33.9 ± 4.8	34.9 ± 5.3
Waist circumference (cm)	116.4 ± 11.6	111.4 ± 15.3
Hip circumference (cm)	117.5 ± 12.4	122.1 ± 14.3
Ratio waist/hip (cm)	0.97 ± 0.05	0.91 ± 0.07

Table 4. Echocardiographic morphological and functional parameters of left atrium and left ventricle in 56 subjects categorized by BMI

	Overweight n=9	**Class I obesity n=26**	**Class II obesity n=13**	**Class III obesity n=8**	**p**
Age (years)	46.5 ± 9.0	48.8 ± 11.1	47.2 ± 7.7	46.3 ± 8.3	0.888
Sex m/f (%)	33.3/66.7	38.5/61.5	30.8/69.2	37.5/62.5	0.968
Waist circumference (cm)	99.0 ± 8.9	109.8 ± 11.7	120.0 ± 9.9	129.1 ± 12.8	0.0001 Owt *vs.* Class II & Class III Class I *vs.* Class III
Hip circumference (cm)	104.6 ± 4.2	117.9 ± 10.9	125.2 ± 10.3	138.7 ± 9.1	0.0001 Owt *vs.* Class I.

					II & III Class I *vs*. class III
Ratio waist/hip (cm)	0.94 ± 0.09	0.93 ± 0.06	0.96 ± 0.07	0.92 ± 0.08	0.629
LA dimension (mm)	37.1 ± 5.3	39.6 ± 3.8	41.0 ± 5.2	42.7 ± 6.2	0.096
LAV (ml)	56.5 ± 13.9	56.5 ± 10.0	62.2 ± 18.6	69.6± 13.4	0.095
LAVI (ml/m^2)	28.7 ± 5.6	27.7 ± 5.2	27.9 ± 7.6	29.5 ± 6.2	0.896
LAVh (ml/m)	33.0 ± 7.0	33.3± 6.0	35.9 ± 9.8	35.0 ± 7.8	0.083
LAEf (%)	40.6 ± 12.0	46.2 ± 8.5	50.5 ± 11.2	49.4 ± 8.0	0.115
e' septum (cm/s)	7.8 ± 2.5	6.9 ± 1.9	7.3 ± 1.9	8.8 ± 2.5	0.155
e' lateral (cm/s)	11.4 ± 4.1	9.2 ± 3.5	11.4 ± 3.2	10.7 ± 2.5	0.184
e' percentage (cm/s)	9.6 ± 3.1	8.2 ± 2.8	9.4 ± 2.0	9.8 ± 2.1	0.309
E/e' septum	10.7 ± 3.1	12.0 ± 3.1	11.7 ± 3.5	10.7 ± 2.9	0.637
E/e' lateral	7.6 ± 2.6	9.5 ± 3.0	7.8 ± 3.1	8.8± 2.7	0.252
E/e' percentage	8.8 ± 2.3	10.5 ± 2.5	9.2 ± 3.0	9.8 ± 2.6	0.285
PALS (%)	31.1 ± 4.2	29.2± 11.4	30.3 ± 7.9	28.4 ± 5.2	0.928
PACS (%)	15.9 ± 3.7	16.6 ± 6.1	17.2 ± 7.3	14.0 ± 3.8	0.700
LVMi	82.0± 24.9	99.0± 23.8	95.3± 24.9	86.2± 27.6	0.278
RWT	0.39± 0.05	0.44± 0.09	0.43± 0.09	0.41± 0.09	0.457

LAEF: left atrial ejection fraction; LAV=left atrial volume LAVI=left atrial volume indexed to BSA; LAV_h= left atrial enlargement indexed to height; e': tissue velocity measured at the level of the mitral annulus in early diastole with Tissue Doppler; E/e' = ratio between the early diastolic transmitral flow and the speed of movement of the mitral ring in early diastole determined by tissue Doppler; PALS=peak atrial longitudinal strain; PACS=peak atrial contraction strain; s'TDI; LVMi:LV mass indexed; RWT: relative wall thickness

Table 5. Correlations of anthropometric parameters with parameters of LA size and function

	BMI (kg/m2)	**Waist circumference (cm)**	**Hip circumference (cm)**	**Ratio waist/hip**
LA dimension (mm)	r=0.331; p=0.013	r=0.473; p=0.0001	r=0.244; p=0.070	r=0.352; p=0.008
LAV (ml)	r=0.310; p=0.020	r=0.451; p=0.001	r=0.469; p=0.0001	-
LAVI (ml/m^2)	-	-	r=0.264; p=0.049	-
LAVh (ml/m)	-	r=0.378; p=0.004	r=0.469; p=0.0001	-
LAef (%)	r=0.283; p=0.035	r=0.271; p=0.043	r=0.310; p=0.020	-
LVMi	-	r=0.231; p=0.087	-	-

LAEF: left atrial ejection fraction; LAV=left atrial volume LAVI=left atrial volume indexed to BSA; LAVh= left atrial enlargement indexed to height; p-value < 0.05 statistical significance r = Pearson correlation coefficient

To determine the role of obesity and its expression parameters (BMI, waist circumference, hip circumference, and their ratio) as independent predictive factors in the occurrence of echocardiographic changes in the morphology and function of the LA, we performed a linear regression analysis with the obesity variables normalized for age and sex. The analysis showed that hip circumference was an independent predictor of increasing maximal LAV (B=0.476; p=0.0001; 95%CI 0.231-0.721) (Figure 1A), LAVI (B=0.114; p=0.049; 95%CI 0.000-0.227) (Figure 1B), and LAVh (B=0.266; p=0.0001; 95%CI 0.129-0.403) (Figure 1C). Accordingly, an increase of nearly 0.5% in hip circumference results in an increase of one unit ml in maximal LAV, an increase of nearly 0.1% in hip circumference increases maximal LAVI by one unit ml, and an increase of nearly 0.3% in hip circumference increases maximal LAVh by one unit ml.

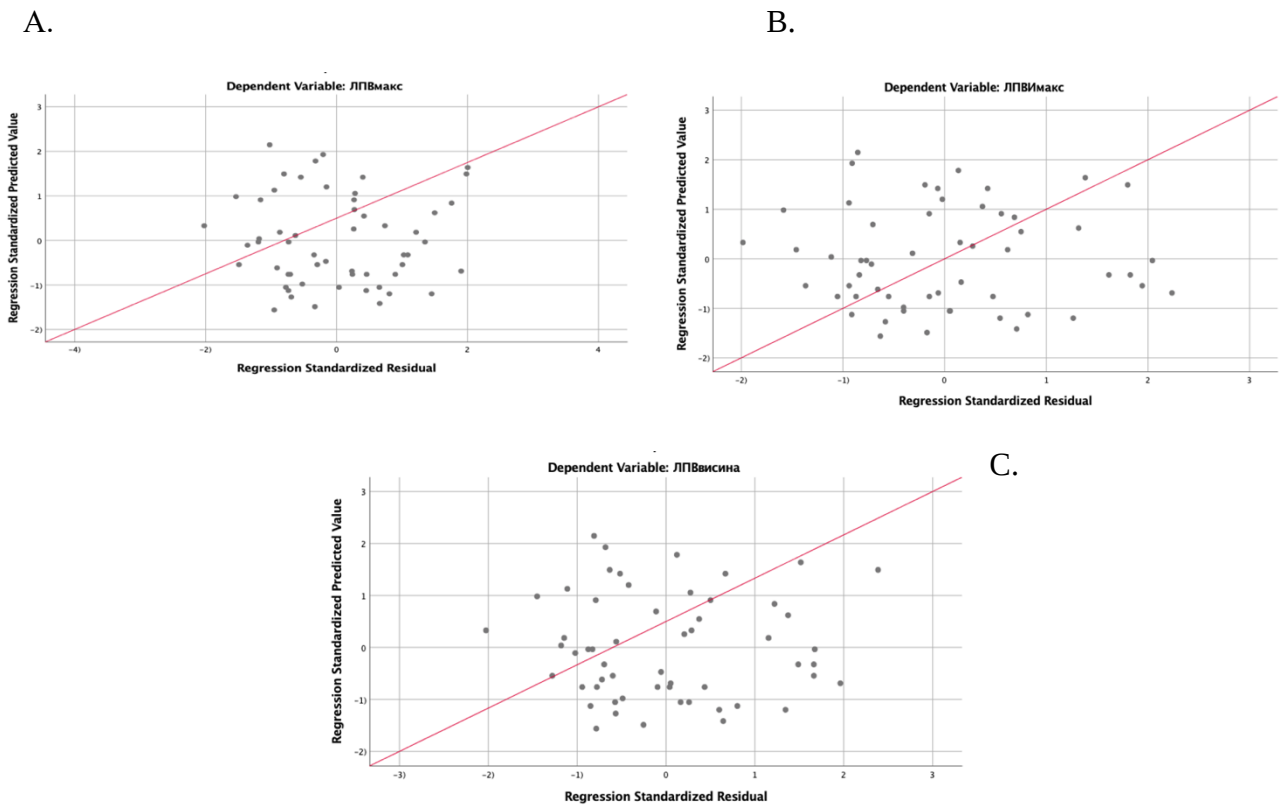

Fig. 1. A graphic illustration of the effect of hip circumference as a predictor of increased peak LA volume (A), LAVI (B), and LAVh (C)

Reproducibility

In order to assess the reproducibility as well as reliability of LA strain measurements, we calculated the intra-class correlation coefficient (ICC) by assessing 20 randomly selected images seen in two different occasions by the same investigator. The Intraclass Correlation Coefficient (ICC) for LA strain measurements was 0.911 (95%CI 0.739-0.970).

Discussion

Obesity is a significant etiological factor in atrial remodeling[43]. Atrial remodeling is the underlying cause of atrial cardiomyopathy (AP), which has recently been defined by a consensus of several cardiology societies as a combination of structural, contractile, and electrophysiological alterations of the atria that have a potential to cause clinically relevant manifestations[1]. Enlargement of the LA is a clinical hallmark of structural remodeling caused by volume and pressure load of the LA; accordingly, LAV is a reliable biomarker for evaluation of diastolic dysfunction[44].

Comparative studies have demonstrated that obese and overweight people have greater LA dimensions and volumes than people of normal weight[45-47]. Also, these studies have demonstrated that there is a dose-dependent relationship between BMI and LAE. Our findings are in line with the data presented in the literature. Left atrial dimensions were increased in all categories of obesity. Regarding volume values, we observed increased values for volume when was indexed for height, but not when indexed for body surface area. Left atrial enlargement is a physiological adaptation process conditioned by an increased intravascular and stroke volume, which occurs in response to the metabolically active adipose tissue requirements. However, at the same time, LAE in obesity may be pathogenic as a result of several factors including pressure load on the LA (diastolic dysfunction and LV

hypertrophy), effects of adipose tissue mediators and fatty acids and the activation of various neurohormonal pathways[3-14]. Therefore, LAV is not an appropriate marker as it does not distinguish between these two forms of remodeling. According to Aiad *et al.*[49], LAE in obesity should be considered in the context of left ventricular (LV) remodeling rather than just as absolute volume. In their study, they showed that LAE in obese subjects was proportionate to LV enlargement and associated with eccentric remodeling[49]. A LAE disproportionate to LV was related to increased LV mass and thickness of LV's posterior wall. Aside from the hemodynamic factors, it is crucial to highlight that LAE is prevalent in obese population even when there is no associated cardiovascular disease or diastolic dysfunction[49].

The use of anthropometric measures to index LA allows for the differentiation of normal from pathological LAE. Left atrium increases in parallel with an increase in body dimensions. However, the link between heart and body size is not linear, and they do not increase in parallel[50]. The isometric indexing of LA volume with body surface area is the most commonly used metric method[51], but it underestimates the effect of obesity on LA. An allometric model that indexes LA to height has a dose-dependent relationship with BMI, E/E', and comorbidities and best depicts LAE in obesity[52-53]. Furthermore, height is correlated with metabolic adipose tissue. Our analysis appear to support these studies. As BMI increased, LAV volume indexed for height increased, however LAV indexed for body surface area did not.

Several studies indicate that BMI may predict LAE[46,48,55-56]. The study conducted by Ayer *et al.*[46] on 2042 obese patients revealed that BMI was a strong and independent predictor of LAE. Likewise, McManus *et al.*[55] during a 16-year follow-up of 4403 individuals discovered a positive correlation between LA dimensions and several factors, including BMI. Age, male gender, systolic blood pressure, and antihypertensive medication all showed out as important variables in this study[55]. Another prospective study[56] investigating the variables that affect LA remodeling over aging found that obesity was the most powerful predictor of LAE, even outperforming arterial hypertension statistically[56]. Posterior wall thickness of LV, dimensions and function of LV, age, and gender also were independent predictors of LAE[46,48]. A correlation between BMI and LAE was established in our study and hip circumference appeared as a predictor of increased LAV, LAVI and LAVh.

Because LAV represents the long-term hemodynamic alterations to which LA is exposed, it cannot be used to identify LA remodeling in the early stages of obesity. The phase function of LA is an echocardiographic parameter that is becoming important in echocardiographic practice as alterations in LA function may precede structural LA remodeling[57]. Furthermore, several studies have shown that LA function is an important cardiovascular prognostic marker [28,59]. Myocardial deformation of LA during the period when the LA function as a reservoir (PALS) is the first to be altered by obesity[54]. Studies have demonstrated an inverse relationship between PALS and BMI[27,58]. The pump function of LA, presented by PACS, is initially increased as a compensatory response, but it gradually declines[58]. A deterioration in pump function is thought to have a crucial role in the development of heart failure in obesity[27,58,59]. In our analysis, we found lower values for PALS and PACS. This might be a result of a longer duration of obesity in our patients.

Conclusion

According to our findings, we conclude that 2D speckle tracking is a sensitive method for detecting subclinical myocardial alterations. The findings of myocardial deformation method might have a substantial impact on current clinical practice. The method of atrial speckle tracking is an eligible screening tool that deserves to be used in clinical practice,

because timely diagnosis of obesity-related atrial cardiomyopathy enables active promotion and timely implementation of therapeutic measures to protect cardiovascular health.

Conflict of interest statement. None declared.

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