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Obesity-related cardiovascular behavior in children

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Abstract. – OBJECTIVE: Obesity is a chronic metabolic disorder and may associate with cardiovascular geometrical, structural and functional changes. The aim of this study is to assess the relationship between body mass index (BMI), body surface area (BSA) and arterial-ventricular elasticity (Ea and Ees respectively) and cardiovascular coupling and myocardial wall stress and fiber stress in obese children.

PATIENTS AND METHODS: Sixty non-obese healthy children with BMI <85th percentile aged 6-17 years and 65 age and sex-matched children with BMI of ≥95th percentile, were included in the study. Beside cardiac systolic and diastolic functions, left verntricular (LV) systolic and diastolic dimensions and volumes (LVDs, LVDd, LVVs, LVVd respectively), LV mass (LVM), LV end-systolic pressure (LVESP), meridional end-systolic wall stress (ESWm), myocardial fiber stress (MFS), Midwall Shortening Fraction (SFmid), heart rate corrected circumferential fiber shortening (VCFc), predicted mid wall fiber shortening for a measured fiber stress (mid wall VCFc), right ventricular (RV) and LV work index (RVWI, LVWI), LV relative wall thickness (LVRWT), arterial elastance (Ea), LV end-systolic elastance (Ees) and end-systolic pressure volume relationship (ESPVR) were calculated.

RESULTS: LVDs and LVDd, LV mass (LVM), ESWSm, MFS, SF mid, Midwall VCFc and LVWI found to be significantly (p<0.001) higher, while Ea, Ees, ejection fraction (EF), fractional shortening (FS), VCFc-ESWS, RVWI, ESWSm/LVVs, LV end-systolic pressure (Pes)/LVVs and LVM/LVVd values were significantly (p<0.001) lower among obese group. By increasing age and BMI the Ea and Ees, ESWSm/LVVS and RVWI decrease; while LVDd, LVVd and stroke volume (SV) values increase. There was a reverse-relation between BMI percentiles and EF and FS.

Key Words:
Arterial stiffness, Children, Obesity, Ventricular stiffness.

Introduction

Obesity is associated with cardiovascular geometrical, structural and functional changes[1-5]. There are great number of investigations about biochemical changes in obese children[6-14], but few about arterial and ventricular systolic elastance, myocardial structure, myocardial fiber stress and wall stress. The aim of this study is to assess the relationship between body mass index (BMI), body surface area (BSA) and arterial-ventricular elasticity and cardiovascular coupling and myocardial wall stress and fiber stress in obese children.

Patients and Methods

This investigation designed as a cross-sectional study using mixed linear and multiple regression models. After of Ethics Committee approval of the institution and obtaining the written consent of the parents, 138 children of 6-16 years old consecutively recruited from the outpatient clinic of our department. BMI calculated as explained by Kuczmarski et al[15] and body mass index (BMI) percentiles were calculated based on children's age and sex according to the World Health Organization (WHO) recommendations. Although the whole protocol applied to entire group, 13 subjects with BMI between >85th-<95th percentile accepted as overweight individuals and were excluded from final calculations. One hundred and twenty five children divided into two groups, 60 non-obese individuals with BMI <85th percentile and 65 age and sex-matched children with BMI of ≥95th percentile.

Brachial systolic and diastolic blood pressures (Ps, Pd respectively) were recorded using bilater-

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al triplicate measurements on a rested subject using a validated oscillometric device in supine position. M-mode, two-dimensional echocardiography, and cardiac Doppler studies were performed by single pediatric cardiologist blind to the groups and the individuals. The following parameters were monitored: systolic and diastolic septal thickness, left ventricular (LV) end-diastolic diameter (LVDd, cm), LV end-systolic diameter (LVDs, cm), LV end-systolic volume (LVVs, ml), LV end-diastolic volume (LVVd, ml), LV end-systolic pressure (Pes), LV mass (LVM, g) according to the formula of Devereux and Reichek[16], LV outflow tract (LVOT, cm), time velocity integral for aortic valve (VTIAo, cm), LV ejection time (LVET, sec), LV pre-ejection period; the time interval from Q wave of ECG to the onset point of aortic Doppler flow (PEP), QT offset; the time interval from Q wave of ECG to the offset point of aortic Doppler flow, stroke volume (SV, mL), ejection fraction (EF, %), fractional shortening (FS, %), peak early diastolic flow velocity peak (Peak E, cm/s), peak late diastolic flow velocity peak (Peak A, cm/s), ratio between heights of early and late diastolic flow velocity peaks (E/A ratio), deceleration time (DT, ms), cardiac output (CO, L/min), meridional end-systolic wall stress (ESWm, g/cm^2), midwall shortening fraction (SFmid), heart rate corrected circumferential fiber shortening (VCFc, circ/s), predicted midwall fiber shortening for a measured fiber stress (VCFc-midwall, circ/s), myocardial fiber stress (MFS, g/cm^2), right ventricular (RV) and LV work indices (RVWI, LVWI respectively), LV relative wall thickness (LVRWT, mm).

LV end-systolic elastance (Ees) was calculated by a modified single-beat method developed by Chen et al[17], employing Ps, and Pd, SV, EF, and an estimated normalized ventricular elastance at arterial end-diastole

$$Ees(sb) = \frac{[Pd-(ENd(est)\times Ps\times 0.9)]}{(ENd(est)\times SV)}$$

where:

$$ENd(est)=0.0275-0.165\times EF+0.3656\times(Pd/Pes)+0.515\times ENd(avg)$$

where:

ENd(avg) is given by a seven-term polynomial function: ENd(avg)=–i=0ai×tiNd

where:

ai are (0.35695, –7.2266, 74.249, –307.39, 684.54, –856.92, 571.95, –159.1) for i=0 to 7, respectively.

Our study methodology was based on the equation developed by Chen et al[17]. The equation of arterial elastance (Ea = ESP/SV) was used to calculate Ea, where ESP designates end-systolic pressure and computed as (ESP=0.9×Ps)[18]. End-systolic pressure volume relationship (ESPVR) was calculated using the formula (ESPVR = ESP/(SV/(1.125-(1.25*(PEP/LVET ofset))-SV), where the PEP stands for pre-ejection period. Ea/Ees was accepted as ventriculo arterial coupling (VAC). Entire methods explained in detail elsewhere[19].

Following formulas were used to calculate ESWSm, SFmid, MFS and VCFc-midwall.

$$ESWSm\ (g/cm^2) = \frac{[1.35\ (Pes)\ (LVES)}{[(4)\ (h_{es})\ (1+h_{es}/LVES)]}$$

where the 1,35 is the conversion factor from mmHg to g/cm^2 and Pes calculated as 0,9 x systolic blood pressure.

$$Sfmid = \frac{[(LVED + h_d/2 + s_d/2) - LVES - mwst]}{(LVED+ h_d/2+s_d/2)}$$

where s_d stands for end-diastolic septal thickness and h_d designates LV end-diastolic posterior wall thickness, the *mwst* calculated as ($mwst$ = $((LVED + (h_d + s_d)/2)^3 - LVED^3 + LVES^3)^{0,333}$ – LVES)

$$MFS\ (g/cm^2) = \frac{[(1.35)(Pes)(\ bm)]}{(2hes)}$$

b_m, the midwall minor semiaxis at end-systole computed as $b_m = h_{es}/\ln(LVES/2 + h_{es}) - \ln(LVES/2)$, where h_{es} stands for left ventricular end-systolic wall thickness.

VCFc-midwall = 0.0007x(*MFS*) + 0.65

Statistical Analysis

The statistical analyses were carried out by Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). Variables were expressed as mean±SD. Comparisons of variables were performed using unpaired Student *t*-test. Bivariate associations of the variables were as-

sessed using Pearson's correlation coefficients. To find the parameters that explain the significance of the variance of the dependent variables, stepwise multivariate linear regression analyses was used and p value <0.05 was considered indicate statistical significance.

Results

Demographic distribution of the subjects was shown in Table I. About 71% of the obese individuals showed ≥99th percentile with mean of 99th percentile for whole obese group. About 27% (16/60) of non-obese children showed BMI less than 25th percentile.

Of cardiac parameters Ps, Pd, LVOT, VTI_{Ao}, LVDd, LVDs, LVM, CO, ESWSm, MFS, SFmid, VCFc-midwall and LVWI found to be significantly (p <0.001) higher, while Ea, Ees (sb), EF, FS, RVWI, ESWSm/LVVs, LVEPs/LVVs and LVM/ LVVd values were significantly (p<0.001) lower among obese group. The difference was found statistically significant. VCFc was also lower among obese group but the difference was not statistically significant. LVET, ESPVR, HR, LVRWT and Mitral-E/A mean values exhibited not statistically significant difference between obese and non-obese children (Table II).

The linear regression studies of the relationship between BMI and cardiac parameters revealed that the Ea, $Ees_{(sb)}$, LVOT, VTI_{Ao}, Ps and Pd, LVDd, LVVd, LVM, CO, SV, ESWSm, MFS, VCFc/ESWS ratio, Midwall/VCFc ratio, Cardiac index, RVWI and ESWSm/LVVS, LVEPs/LVVs and LVM/LVVd values change significantly by increasing age and BMI percentiles.

The parameters which explain (R^2) the age and BMI percentiles as independent variables the most were as follows: LVOT (55,4%), LVDd (53.3%), LVVd (49.7%), SV (43.0%), $Ees_{(sb)}$ (41.6%), ESWSm/ LVVS (36.6%), Ea (35.4%) and RV Work index (37.7%). By increasing age and BMI the arterial and ventricular elasticity (Ea and $Ees_{(sb)}$), ESWSm/LVVS and RVWI decrease; while LVOT, LVDd, LVVd and SV values increase. The parameters which explain (R^2) the age and BMI percentiles as independent variables the least were as follows: CO (31.9%), Pd (28.1%), Ps (26.3), LVRWT (21.6%) and FS (19.2%). Independent from the age, there was a reverse-relation between BMI percentiles and EF and FS. By increasing BMI percentiles, EF (r=-.256) and FS (r=-.272) values decrease, but only 6% and 7% of changes in EF and FS respectively were explained independent from BMI percentiles. Independent from BMI percentiles, there was a positive relation between age and LVET and negative relation with ESPVR (Table III). VAC ratio did not change with BMI and BSA significantly. Although relative wall thickness showed not significant difference between the groups, a significant correlation at 0.05 level was found with age and BMI. There was no significant difference in PEP/ET and PEP/QT offset values among the groups, while Pes/LVVs and LVM/LVVd values showed significant differences.

Table I. Demographic properties distribution of the age groups.

Age groups (months)	Non-obese n (%)	Obese n (%)	Total n (%)
72 –< 84	7 (70.0)	3 (30.0)	10 (8.0)
84 – < 108	15 (65.2)	8 (34.8)	23 (18.4)
108 – < 144	10 (35.7)	18 (64.3)	28 (22.4)
144 – < 180	14 (36.8)	24 (63.2)	38 (30.4)
180 – 204	14 (53.8)	12 (46.2)	26 (20.8)
Total	**60 (48.0)**	**65 (52.0)**	**125 (100.0)**
Demographic properties			***p*-value[a]**
BMI PER - mean (SD)	47.69 (24.93)	99.05 (1.14)	< .001
Height (cm) - mean (SD)	142.28 (20.69)	153.08 (14.00)	.001
Weight (kg) - mean (SD)	37.54 (15.09)	66.27 (18.10)	< .001
Age (years) - mean (SD)	11.02 (3.68)	11.72 (2.85)	.241

[a]Independent Student's t-testi

Table II. Cardiac parameters among non-obese and obese children

Cardiac parameters	Non-obese (n=60)		Obese (n=65)		Difference mean	*t*-test[a] *p*-value
	Mean	SD	Mean	SD		
Cardiac index[b]	3.51	0.86	3.06	0.77	0.45	0.003
CO	4.15	1.3	5.1	1.53	-0.95	< .001
Ea	2	0.47	1.62	0.41	0.38	< .001
$Ees_{(sb)}$	2.82	0.74	2.15	0.75	0.67	< .001
EF	0.77	0.06	0.731	0.078	0.039	0.005
ESPVR	18.29	8.76	18.31	12.17	-0.02	0.994
ESWSm	167.4	54.71	217.82	66.11	-50.42	< .001
ESWSm/LVVS	7.93	1.84	6.78	1.31	1.15	< .001
FS	0.39	0.06	0.36	0.059	0.03	0.004
HR	82.88	12.16	82.26	12.36	0.62	0.778
LVWI	39.09	9.06	44.01	9.34	-4.92	0.003
LVDd	4.03	0.5	4.53	0.5	-0.5	< .001
LVET	289.3	34.71	280.43	34.05	8.87	0.152
LVM	56.8	12.82	64.22	16.05	-7.42	0.005
LVOT	1.68	0.23	1.89	0.22	-0.21	< .001
LV Vd	72.74	21.27	95.57	24.54	-22.83	< .001
MFS	226.74	57.88	283.86	68.94	-57.12	< .001
Mitral-E/A	1.88	0.33	1.83	0.33	0.05	0.412
Pd	63.51	9.02	72.45	8.18	-8.94	< .001
Ps	108.78	11.85	119.32	9.93	-10.54	< .001
RWT	0.24	0.07	0.243	0.063	-0.003	0.613
RVWI	4.64	1.07	2.98	0.63	1.66	< .001
SFmid	0.16	0.08	0.186	0.041	-0.026	0.045
SV	52.07	14.76	70.26	17.9	-18.19	< .001
VCFc	0.01	0	0.006	0.001	0.004	0.255
VCFc-midwall	0.81	0.04	0.849	0.048	-0.039	< .001
VTI_{Ao}	22.77	2.68	24.75	3.03	-1.98	< .001

[a]Student's *t*-test (for independent samples). [b]Cardiac output index: cardiac output/BSA, BP: blood pressure, CO: cardiac output, E/A: the early diastolic flow velocity peak to late diastolic flow velocity peak ratio, Ea: arterial elastance, Ees(sb): left ventricular elastance at end-systole derived by single-beat technique, EF: ejection fraction, ESPVR: end-systolic pressure volume relationship, ESWSm: meridional end-systolic wall stress, FS: fractional shortening, HR: heart rate, LV: left ventricle, LVDd: left ventricular end-diastolic diameter, LVET: left ventricular ejection time, LVM: left ventricular mass, LVOT: left ventricular outflow tract, LVVd: left ventricular end-diastolic volume, LVVs: left ventricular end-systolic volume, LVWI: left ventricular work index, MFS: Fiber stress, Pd: diastolic blood pressure, Ps: systolic blood pressure, SFmid: midwall shortening fraction, RVWI: right ventricular work index, RWT: relative wll thickness, SV: stroke volume, VCFc: heart rate corrected midwall circumferential fiber shortening, VCFc-midwall: predicted midwall fiber shortening for a measured fiber stress, VTIAo: time velocity integral for aortic valve, WT: wall thickness.

Discussion

Obesity accompanies with cardiac and vascular structural and functional changes[3,4]. We found that the arterial and LV elasticity decrease and stiffness increase by increasing BMI in obese children. We previously reported that the same cardiac parameters exhibit the same tendency by increasing the age of the healthy children and adolescences[19].

Contractility and loading (preload and afterload) dependent indices, reflecting ventricular global performance, can be estimated by measuring chamber mechanics like SF and FS. The ventricular contractility and myocardial performance may also affected by chamber geometry which need to be identified by measuring ESWSm, VCFc-midwall and MFS. ESWSm accepted as afterload (no more shortening point). ESWSm, which is dependent on both chamber shape and mass/volume ratio, demonstrates the forces opposing predominantly meridional and circumferential planes. This is an index of total forces per unit of myocardium, thus may cause an under estimation in true afterload. MFS as representative of myofiber afterload, is more accurate index of

afterload in hypertrophied or dilated LV[20]. SFmid as systolic ejection index of deeper layers of myocardium provides more physiologically appropriate measurements of LV in wall thickness and conditions like LV concentric hypertrophy and provides information to assess the myocardial performance[20]. In this study SFmid was higher but not significant among obese subjects.

We found ESWSm, MFS, VCFc-midwall being higher in obese individuals. The relationship between ESWSm and VCFc is one of the best echocardiographic measurements providing information on myocardial mechanics. As our findings exhibit, the relationship between VCFc and ESWSm is linear over physiologic state, independent of HR and preload and incorporates afterload, making it responsive to changes in ventricular inotropy[21,22]. Although both PEP/ET and PEP/QT offset ratios affected by the age of the children, we found no significant difference between the obese and non-obese individuals. BMI percentiles did not affect these ratios. On the oth-

Table III. The cardiac parameters relationship between BMI percentiles and age.

Cardiac parameters	BMI (percentiles)		Age (months)		Multiple regression	
	r	B[a]	r	B[a]	Adj. R^2	*p*-value
Cardiac index[b]	-.242**	-.006*	-.239**	-.005**	.090	.001
Cardiac output	.317**	.013**	.511**	.018**	.319	< .001
Ea	-.379**	-.005**	-.508**	-.006**	.354	< .001
Ees (sb)	-.405**	-.009**	-.552**	-.011**	.416	< .001
EF	-.256**	-.001**	.072	.000	.060	.008
ESPVR	-.031	.005	-.417**	-.113**	.161	< .001
ESWSm	.378**	.758**	.228**	.317*	.165	< .001
ESWSm/ LVVS	-.365**	-.017**	-.529**	-.021**	.366	< .001
FS	-.272**	-.001**	.081	.000	.071	.004
HR	-.036	-.008	-.151	-.046	.007	.238
LVWI	.227**	.066*	.148	.030	.052	.014
LVDd	.456**	.007**	.622**	.008**	.533	< .001
LVET	-.053	-.086	.217*	.198*	.037	.036
LVM	.262**	.113**	.296**	.103**	.127	< .001
LVOT	.375**	.002**	.685**	.004**	.554	< .001
LVVd	.447**	.320**	.598**	.362**	.497	< .001
Mitral-E/A	-.051	-.000	-.048	-.000	-.012	.760
MFS	.401**	.852**	.251**	.373**	.192	< .001
Pd	.407**	.118**	.387**	.085**	.281	< .001
Ps	.401**	.142**	.379**	.104**	.263	< .001
RVWI	-.592**	-.022**	-.254**	-.006**	.377	< .001
RWT	.043	1.790	.478**	.001**	.216	< .001
SFmid	.127	.000	.205*	.000	.037	.037
SV	.452**	.242**	.530**	.232**	.430	< .001
VCFc	-.157	-6.088	.040	1.682	.012	.177
VCFc/ESWS	-.378**	-.758**	-.228**	-.317*	.165	< .001
VCFc-midwall	.401**	.001**	.251**	.0001**	.192	< .001
VTIAo	.346**	.036**	-.185*	-.017**	.156	< .001

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), r: Bivariate correlation value. B: Unstandardized Coefficients. R2: The adjusted coefficient of determination. a BMI (percentiles) and age (months) variables both were taken multiple regression analysis. BP: blood pressure, CO: cardiac output, E/A: the early diastolic flow velocity peak to late diastolic flow velocity peak ratio, Ea: arterial elastance, Ees(sb): left ventricular elastance at end-systole derived by single-beat technique, EF: ejection fraction, ESPVR: end-systolic pressure volume relationship, ESWm: meridional end-systolic wall stress, FS: fractional shortening, HR: heart rate, LV: left ventricle, LVDd: left ventricular end-diastolic diameter, LVET: left ventricular ejection time, LVM: left ventricular mass, LVOT: left ventricular outflow tract, LVVd: left ventricular end-diastolic volume, LVVs: left ventricular end-systolic volume, LVWI: left ventricular work index, MFS: myocardial fiber stress, Pd: diastolic blood pressure, Ps: systolic blood pressure, RVWI: right ventricular work index, RVWT: Relative wall thickness, SFmid: midwall shortening fraction, SV: stroke volume, VCFc: heart rate corrected midwall circumferential fiber shortening, VCFc-midwall: predicted midwall fiber shortening for a measured fiber stress, VTIAo: time velocity integral for aortic valve, WT: wall thickness.

er hand, the LVVPs/LVVs and LVM/LVVd ratios were significantly different ($p<0.001$) and in regression analyses both ratios were affected by BMI and the age.

Ees as a measure of contractility, may also influenced by chamber geometry and passive myocardial stiffening[23,24]. Chirinos et al[25] reported that after adjustment for age and sex, a progressive increase in indexed systemic vascular resistance, effective arterial and ventricular end-systolic elastance, and a decrease in total arterial compliance were seen from normal weight to obesity. They also underlined that the arterial load relates to body size in an allometric fashion, calling for scaling with the use of appropriate powers. They concluded that the obesity exerts adverse effects on arterial load and ventricular stiffening that go beyond the normal relationship with body size. Harada et al[26] studied obesity related arterioventricular stiffening in children and showed that the higher BMI is associated with increases in arterial, ventricular systolic, and ventricular diastolic stiffness in children while the VAC ratio remains without significant changes. Koopman et al[8] showed that the ratio of Ea/Ees was lower in obese children than non-obese individuals. Our study demonstrated an inverse relationship between BMI and arterial and LV elasticity. However, we found any significant change in Ea/Ees ratio between the groups. It has been shown that the aortic stiffness and pulmonary artery stiffness were also significantly increased in children who were at risk for obesity compared with control children ($p < 0.001$) and have subclinical LV and RV dysfunction[27].

In comparison with older children the healthy children younger than two years of age demonstrate higher MFS and VCFc-midwall. Calabrò et al[28] revealed that there was an inverse linear relation between MFS and ESWS and between VCFc and ESWS in both healthy children younger and older than two years of age.

In pediatric age echocardiographic evaluation of LV systolic function, it is usually based on indexes obtained by measurements at the endocardial level. It is suggested that in the presence of ventricular hypertrophy, the evaluation of LV systolic function based on indexes obtained by measurements at the endocardial level may lead to an overestimation of systolic function. Crepaz et al[29] assessed the developmental changes of LV systolic mechanics measured at the endocardial and midwall levels. They found that blood pressure, LV afterload, volume and mass increased, whereas the mass/volume ratio remained stable during growth. FS and mean VCFc at the endocardial level decreased and showed an inverse relation to afterload. SFmid and VCFc were lower during the first months and did not change during the first year of life. They concluded that LV volume and LVM increase with age, mass/volume ratio remains almost constant while afterload increases. Endocardial systolic function indexes are higher in the first period of life.

Conclusions

Arterial and LV stiffness, LVM, wall stress increase and contractility and VCFc-midwall decrease by increasing BMI and BSA in obese children which all exhibit risk factor for developing cardiovascular dysfunctions in later years.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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