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RESEARCH ARTICLE

ROLE OF URIC ACID IN CARDIAC CHANGES IN OVERWEIGHT AND OBESE CHILDREN.

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Abstract

Background: High serum uric acid (UA) levels appear to contribute to an increase in blood pressure (BP) in obese adolescents and may amplify the cardiac volume overload effects of obesity with pressure overload. Association between UA and ejection fraction (EF) is still controversial. Some studies showed negatively correlations, others did not found any correlation. So far, no data have been published regarding the influence of UA levels on structural and functional changes of the LV in children with obesity.

Objective: The aim of our study was to assess the influence of UA levels on LV structure and function in overweight/obese children.

Study groups and methods: In 25 (mean age 13.0 ± 2.3) overweight/obese subjects and 24 lean controls, BP, fasting plasma glucose, insulin, and UA were measured. LV structural and functional parameters were measured by echocardiography.

Results: In overweight/obese children UA correlates with LV diastolic volumes and LV systolic function but not with LVM whereas in children without obesity UA correlates with LVM and LV diastolic function.

Conclusion: The present study demonstrates a positive correlation of UA with EF and left atrium and LV volume in volume overload due to obesity in children. These conclusions require further investigation.

Introduction:-

Obesity is associated with a shortened life expectancy mainly because of increased risk for cardiovascular (CV) disease. Uric acid (UA) levels have been shown to be a good marker for metabolically unhealthy obesity i.e. those with features of metabolic syndrome and elevated CV risk factors in adolescence and adulthood (1).

High UA levels are a risk factor for hypertension in adults (2). Several studies have assessed the relationship between UA levels and LV mass (LVM) in adults with hypertension (3,4). The development of LV hypertrophy (LVH) in hypertensive adults with high UA levels can at least partially explain the elevated CV risk observed in

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these patients, as LVH is a strong predictor of CV disease (5). Allopurinol caused regression of LVM in patients with type 2 diabetes and LVH (6). High UA levels also appear to contribute to an increase in BP in obese adolescents (7) and may therefore amplify the cardiac volume overload effects of obesity with pressure overload.
UA may also affect LV function. Experimental studies have shown that high UA leads to cardiac fibrosis and LV diastolic dysfunction (8). Hyperuricemia was associated with worse cardiac function, such as increased right atrial pressure and decreased cardiac index in patients with primary pulmonary hypertension, and increased atrial pressures in patients with ischemic heart disease or dilated cardiomyopathy in small case series (9). Increased serum UA levels may contribute to cardiac dysfunction through effects on endothelial function and inflammation. UA inhibits nitrogen oxide (NO) production by vascular endothelial cells and their proliferation and migration (10).

So far, no data have been published regarding the influence of UA levels on structural and functional changes of the LV in obese children. The aim of our study was to assess the relation of UA levels and structural and functional changes of the LV in children with obesity compared to lean controls.

Methods:-

This was an observational study conducted in the Department of Metabolic Disease of the Pediatric Clinic at the Children Hospital, Kosice. All participants were referred for evaluation of obesity. Twenty five Caucasian overweight/ obese subjects (13.0 ± 2.3 years of age, 9 female) with Body Mass Index (BMI) ≥ 85 percentile for age and gender were included in the study and were compared with 24 lean healthy subjects (12.9 ± 3.4 years of age, 12 female). Subjects with secondary causes of obesity were excluded and none were taking medications or had a history of cardiovascular disease. Age- and gender-matched children were children with BMI< 85th percentile for age and gender (11) BMI was calculated as weight (kg) divided by the square of height (m) and BMI percentiles and waist circumference (WC) were measured according to WHO recommendations (12). Blood pressure (BP) was measured with a standard mercury sphygmomanometer and a cuff appropriate for the size of the child's upper right arm. Systolic and diastolic BP were measured three times after 10 min rest in the supine position, and the average of the 3 measurements was calculated.

Echocardiographic examination was done with a Vivid 5 echocardiograph, using the 3.5MHz probe S611, by the same cardiologist. The echocardiographic examination included a comprehensive 2-D examination, colour and spectral Doppler examination and complete examination in M-mode acquired from 2-D projection. The techniques used to measure LV inner diameter, enddiastolic and endsystolic interventricular septal thickness (IVS dias, IVS sys) and LV posterior wall thickness (PWTh dias, PWTh sys) comply with the recommendations of American Society of Echocardiography. Pressure half time from blood flow Doppler evaluation (PHT), LV volume in systole and diastole, myocardial performance index (MPI), LV mass (LVM), LV mass indexed to body height$^{2.7}$ (LVMIV), left atrial (LA) M mode, ejection fraction (EF), stroke volume (SV) were calculated. The recommendations of the American Society of Echocardiography were used to determine diastolic function and its individual indexes (13). The pulse Doppler examination of flow through the mitral valve was used to obtain the following parameters: peak early transmitral filling wave velocity (E-wave), peak late transmitral filling wave velocity (A-wave), deceleration time of early diastolic filling (DT), and isovolumic relaxation time (IVRT).

Fasting blood samples were drawn after 12 h overnight fast. Plasma glucose was measured enzymatically using a Siemens ADVIA. Fasting serum insulin was measured by a sandwich ECLA method using a Roche Modular Analytics E170 analyzer. UA was measured by photometric kinetic method using the Siemens ADVIA biochemical autoanalyzer. The homeostasis model assessment of insulin resistance (HOMA index) was calculated according to the standard formula (14).

Statistical analysis:-

Data were processed using methods of descriptive and inductive statistics, depending on the type and number of variables monitored. For the purpose of inductive statistics, we assumed that our data represent a random sample of the relevant population. The first step was a one-dimensional analysis, the tabulation of all monitored variables using frequency tables. The second step was a two-dimensional analysis, the assessment of pairs of monitored variables. To compare numerical and categorical variables, analysis of variance was used to determine the statistical significance of differences, if the distribution of variables was normal. All calculations were performed using version 8.0 of statistical Package for the Social Sciences software. The significance level was set to the traditional $p< 0.05$.

Results:-

Anthropometric, clinical and biochemical parameters

Body weight (BW), BMI, BMI percentile, BMI Z-score, WC, systolic and diastolic BP, HOMA index and insulin levels were all significantly higher in overweight/obese subjects compared to lean controls. UA tended ($p=0.16$) to be higher in overweight/obese subjects (Table 1).

Echocardiographic parameters

Regarding structural echocardiographic parameters (Table 2a), overweight/obese subjects had significantly higher IVS dias, LV dias, LV sys and LA 2D area, LVM and LVMIV. Functional diastolic echocardiographic parameters showed increased A wave and IVRT, and significantly decreased DT and PHT in overweight/obese children (Table 2b). LV volumes and SV were also significantly higher in overweight/obese children (Table 2b).

In both overweight/obese and lean control groups structural echocardiographic parameters correlated with BW and BMI. Only in obese children WC correlated with IVS dias, LV dias, PWTh dias, and with LVM (Table S1). Only overweight/obese children showed negative correlations of E wave with BW, WC and BMI (Table S1). Most functional systolic echocardiographic parameters correlated with BW and BMI but only in overweight/obese children correlations were present between WC and LV and SV volumes (Table S1).

In both lean controls and overweight/obese children there were significant positive correlations between systolic BP and structural echocardiographic parameters and LV volume dias and SV (Table S1). Diastolic BP followed the same pattern (data not shown).

Correlations of uric acid and other biochemical parameters with echocardiographic parameters

UA correlated with BW in both lean controls ($r=0.67$, $p<0.01$), and in overweight/obese children ($r=0.50$, $p<0.05$).

In lean controls, UA positively correlated with IVS dias, IVS sys and LVM, and negatively with A wave (Table S2). In overweight/obese children UA correlated with LA area (Table S2), LV diastolic volume, SV and EF (Table S2). Statistical significant differences between the two study groups were only found for the correlation between UA and SV (Figure 1, Figure 2).

HOMA did not correlate with any of LV functional parameters in obese and lean controls. Only in lean controls plasma glucose correlated with diastolic functional parameters (data not shown).

Discussion:-

This appears to be the first study focusing on the relation of UA levels and echocardiographic parameters of cardiac structure and function in overweight/obese children. We demonstrate that in overweight/obese children UA correlates with LV diastolic volumes and LV systolic function but not with LVM whereas in children without obesity UA correlates with LVM and LV diastolic function.

Obesity represents a chronic volume overload for the heart and - as expected - significant increases in LA and LV volumes and LVM were observed in obese children (15, 16). Studies analyzing the relationship between UA levels and LVM in adults have shown variable results. A positive correlation between UA levels and LVM was identified in several studies in adults (17) but not in other studies in adult patients with hypertension (3,5). Participants of Framingham Offspring Cohort, in the highest serum UA quartile had significantly higher LV wall thickness, LV end-diastolic diameter and LVM, compared with those in the lowest quartile (18). Conflicting conclusions regarding the relationship between UA levels and LVM may be partially explained by the methodology used (3).

Experimentally, UA induces cardiomyocyte growth and interstitial fibrosis of the heart, partially by activation of the renin-angiotensin system (RAS) (19). The RAS may cause LVH and cardiac fibrosis through an increase in BP, a direct effect of angiotensin II on myocardial myocytes and indirectly via aldosterone (20). UA may also increase LVM by inducing endothelial dysfunction and proliferation of smooth muscle cells by increased activity of xanthine oxidase and oxidative stress (21). Increased oxidative stress may increase degradation of endothelium-derived NO and cause impairment of vascular tone regulation (22). UA also may activate inflammatory mediators, and stimulate mitogen-activated protein kinases, which may contribute to cardiac hypertrophy (23). These mechanisms may function differently in obese children, because in our group of children a correlation between LVM and UA was

present only in non-obese children. Moreover, the normal/mildly elevated UA levels correlated with BW, and when taking BW into account UA levels did not correlate with LVM in either group, suggesting that UA levels did not directly affect the heart. Impact of UA on LVM may require a longer duration of obesity, more significant hyperuricemia and/or longer duration (1).

Higher serum UA levels might also contribute to cardiac dysfunction. Patients with congestive heart failure (HF) and increasing filling pressures had significantly higher serum UA levels and serum UA levels correlated with echocardiographic parameters of diastolic function (24). Patients with gouty tophi had a significantly thicker LV interventricular septum and posterior wall and increased LA volume index reflecting LV diastolic dysfunction (25) Hyperuricemia is an independent predictive factor for LV diastolic dysfunction also in patients with chronic kidney disease (26). Findings of these studies are consistent with our results in lean controls in whom serum UA correlated with parameters of LV structure and LV diastolic function but not with LV volumes.

On the other hand, this is the first study showing a correlation between UA and LV volumes due to obesity induced volume overload. Codoñer-Franch et al, (27) showed a higher concentration of NO production markers, which correlated with the increased markers of oxidative stress in obese children. We suggest that increased levels of NO in early stages of obesity in childhood could be involved in different effects of UA on LV structure and subsequent diastolic function at this age.

Association between serum UA and EF is still controversial. Some studies showed negatively correlations (28, 29) others did not found any correlation (26, 27, 28). In the present study a positive correlation was observed between UA and EF, ($p<0.05$ in the presence of obesity). Tavil et al used issue Doppler imaging for the evaluation of myocardial performance index (MPI) (30). MPI in patients with arterial hypertension and hyperuricemia was significantly higher than in hypertensive patients without hyperuricemia. Systolic and diastolic BP were significantly higher in obese in the present study and BP may play an important role in the relationship between UA and EF.

Conclusion:-

The present study demonstrates a positive correlation of UA with EF and LA and LV volume in volume overload due to obesity in children. We did not confirm an influence of UA on LVM and on LV diastolic function in the presence of obesity. These conclusions require further investigation involving a larger cohort of children.

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Conflict Of Interest

The authors declare no conflict of interests

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Schusterova I. conceived experiments, Schusterova I. and Leenen FHH. carried out a data analyses and interpretation. Tohatyova A. carried out a literature review and data collection. Artemiou P. carried out generation of figures, Takacova J. and Takac L. statistically analyzed data. All authors were involved in writing the paper and ha final approval of the submitted and published version.

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Table 1:-Anthropometric, clinical and biochemical characteristic

Variables	**Overweight/Obese (BMI ≥ 85 percentile) N=25**	**Lean control (BMI < 85 percentile) N=24**	**p- value**
Age (years)	13.0 ± 2.3	12.9 ± 3.4	ns
Body weight (kg)	72.3 ± 19.6	50.5 ± 14.3	< 0.01
Height (cm)	164 ± 16	161 ± 13	ns

BMI (kg/m2)	27.4 ± 3.5	18.8 ± 3.1	< 0.01
BMI percentile	94.3 ± 3.5	36.2 ± 2.8	< 0.01
BMI Z-score	2.09 ± 0.51	-0.38 ±1.01	< 0.01
Waist circumference (cm)	95.5 ± 12.6	73.1 ± 8.8	< 0.01
Uric acid (umol/l)	321 ± 67	282 ± 69	ns
Glucose (mg/dl)	89 ± 9.1	89 ±8.2	ns
Insulin (IU/L)	15.4 ±7.2	8.0±4.2	< 0.05
HOMA-index	3.5 ± 2.0	1.9±1.9	<0.01
Systolic BP (mmHg)	133 ± 16	120 ± 17	<0.05
Diastolic BP (mmHg)	80 ± 11	70 ± 7	<0.01

Data are shown as the mean ± standard deviation (SD), ns- not significant BMI, body mass index; HOMA index, homeostasis model assessment of insulin resistance; BP, blood pressure.

Table 2a:-Structural echocardiographic parameters

Parameter	**Overweight/Obese (BMI ≥ 85 percentile) N=25**	**Lean control (BMI < 85 percentile) N=24**	**p- value**
IVS dias (cm)	0.91 ± 0.20	0.75 ± 0.18	< 0.01
IVS sys (cm)	1.44 ± 0.40	1.30 ± 0.26	ns
PWTh dias (cm)	0.82 ± 0.15	0.73 ± 0.16	0.06
PWTh sys (cm)	1.40 ± 0.29	1.37 ± 0.32	ns
LV dias (cm)	4.85 ± 0.56	4.30 ± 0.50	< 0.01
LV sys (cm)	3.11 ± 0.75	2.62 ± 0.53	< 0.05
LVM (g)	149 ± 10	54 ± 43	< 0.01
LVMIV ($g/m^{2.7}$)	39.6 ± 28.3	10.1 ± 8.3	<0.001
LA 2D area (cm^2)	14.7 ± 3.5	12.4 ± 2.7	< 0.05

Data are shown as mean ± SD, ns- not significant, LA = Left atrium, LV = Left ventricular; IVS dias - Enddiastolic interventricular septum thickness; LV dias Enddiastolic diameter; PWTh dias - Enddiastolic posterior wall thickness; IVS sys - Endsystolic interventricular septum thickness; LV sys - Endsystolic diameter PWTh sys - Endsystolic posterior wall thickness; LVM- LV mass; LVMIV LV mass indexed to body $height^{2.7}$.

Table 2 b :-functional LV systolic and diastolic echocardiographic parameters

	Overweight/Obese (BMI ≥ 85 percentile) N=25	**Lean control (BMI < 85 percentile) N=24**	**p- value**
LV diastolic parameters			
A wave (m/s)	0.60 ± 0.10	0.51 ± 0.11	<0.01
E wave (m/s)	1.02 ± 0.23	0.96 ± 0.11	ns
IVRT (ms)	177.5 ± 70.4	132.7 ± 34.0	< 0.001
DT (ms)	143.1 ± 55.7	186.3 ± 75.1	<0.05
PHT (ms)	42.01 ± 6.3	54.5 ± 22.1	<0.05
LV systolic parameters			

LV volume dias (cm^3)	118.5 ± 34.7	85.3 ± 21.7	< 0.01
LV volume sys (cm^3)	44.1 ± 9.0	36.8 ± 11.0	< 0.05
EF (%)	61 ± 9	56 ± 10	0.09
SV (ml)	74 ± 30	49 ± 19	< 0.01
MPI	0.14 ± 0.52	0.21 ± 0.22	ns

Data shown as mean ± SD, ns- not significant wave - peak early transmitral filling wave velocity velocity; A wave - peak late transmitral filling wave velocity; IVRT - isovolumic relaxation time; DT – deceleration time of early diastolic filling; PHT - pressure half time from blood flow Doppler evaluation; MPI - Myocardial performance index; EF - Ejection fraction; SV - Stroke volume. LV volume dias- LV volume in diastole; LV volume sys- LV volume in systole.

Table S1 (Supporting Table) Correlations of LV structural and LV functional diastolic and systolic echocardiographic parameters and with Blood Pressure (BP) and anthropometric parameters.

	Lean control			**Overweight/Obese**			
Parameter	**Body Weight**	**BMI**	**Syst BP**	**Body Weight**	**Waist Circum.**	**BMI**	**Syst BP**
IVS dias (cm)	r=0.60 p< 0.01	r=0.44 p< 0.05	ns	r=0.51 p< 0.05	p=0.05	p=0.07	ns
IVS sys (cm)	r=0.72 p<0.001	r=0.64 p< 0.01	ns	r=0.48 p< 0.05	p=0.05	p< 0.01 r=0.56	ns
PWTh dias (cm)	r=0.66 p<0.001	r=0.55 p< 0.01	p=0.055	r=0.59 p< 0.01	p=0.05	ns	r=0.55 p<0.05
PWTh sys (cm)	r=0.57 p< 0.01	r=0.49 p< 0.05	ns	r=0.44 p< 0.05	p=0.06	ns	ns
LV dias (cm)	r=0.68 p<0.001	p=0.06	r=0.61 p<0.05	r=0.58 p< 0.01	p=0.05	ns	r=0.58 p<0.05
LV sys (cm)	r=0.48 p< 0.05	ns	r=0.72 p<0.01	ns	ns	ns	ns
LVM (g)	r=0.76 p<0.001	r=0.54 p< 0.05	r=0.57 p<0.05	r=0.72 p<0.001	r=0.55 p< 0.05	p=0.05	r=0.62 p<0.01
LVMIV ($g/m^{2.7}$)	r=0.52	p=0.07	ns	ns	ns	ns	ns
LA 2D area (cm^2)	r=0.71 p<0.001	r=0.56 p< 0.01	ns	r=0.59 p< 0.01	r=0.47 p< 0.05	ns	p=0.06
E wave (m/s)	ns	ns	ns	r= -0.49 p< 0.05	r= -0.47 p< 0.05	r= -0.45 p< 0.05	ns
A wave (m/s)	ns	ns	ns	ns	ns	p=0.06	ns
EF (%)	r=0.55 p< 0.05	p=0.06	ns	r=0.52 p< 0.05	ns	p=0.05	r=0.58 p<0.05
SV (ml)	r=0.79 p<0.001	r=0.69 p< 0.01	r=0.65 p<0.05	r=0.62 p<0.001	r=0.44 p<0.001	r=0.41 p< 0.01	r=0.58 p<0.001
LV sys volume (cm^3)	ns	ns	ns	r=0.68 p<0.001	r=0.56 p< 0.05	ns	ns
LV dias volume (cm^3)	r=0.82 p<0.001	r=0.74 p<0.001	r=0.68 p<0.05	r=0.88 p<0.001	r=0.80 p<0.001	r=0.57 p< 0.01	r=0.77 p<0.001

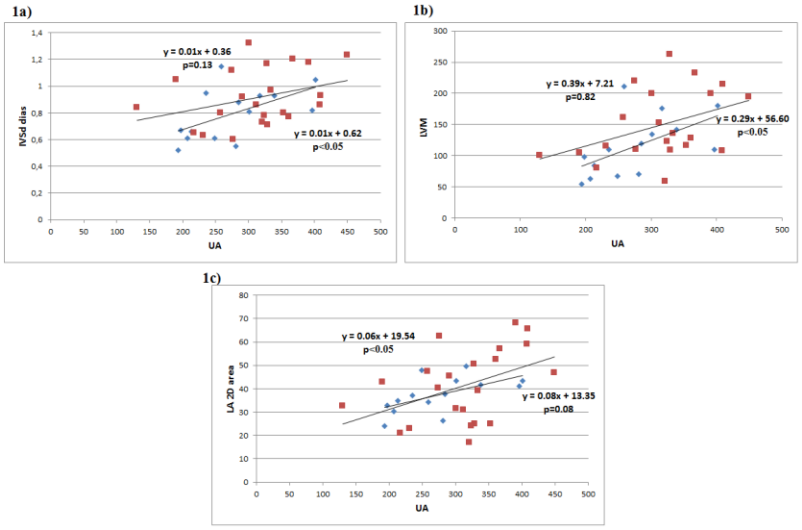
ns- not significant. LA = Left atrium, LV = Left ventricular; IVS dias - Enddiastolic interventricular septum thickness; LV dias Enddiastolic diameter; PWTh dias - Enddiastolic posterior wall thickness; IVS sys - Endsystolic interventricular septum thickness; LV sys - Endsystolic diameter PWTh sys - Endsystolic posterior wall thickness; LVM- LV mass; LVMIV -LV mass indexed to body height$^{2.7}$, E wave - peak early transmitral filling wave velocity velocity; A wave - peak late transmitral filling wave velocity velocity; EF - Ejection fraction; SV - Stroke volume. LV volume dias - LV volume in diastole; LV volume sys- LV volume in systole BMI- body mass index, In lean controls, Waist Circumference showed no correlations

Table S2:-(Supporting Table) Correlations between UA and LV structural and LV diastolic and systolic echocardiographic parameters

	Lean control	**Overweight/Obese**
IVS dias (cm)	r=0.55 p< 0.05	ns
IVS sys (cm)	r=0.70 p< 0.01	ns
LV dias (cm)	p=0.07	ns
LVM (g)	r=0.56 p< 0.05	ns
LVMIV (g/m$^{2.7}$)	p=0.055	ns
LA 2D area (cm^2)	p=0.08	r=0.45 p< 0.05
A wave (m/s)	r= -0.60 p< 0.05	ns
E wave (m/s)	ns	ns
EF (%)	ns	r=0.42 p< 0.05
SV (ml)	ns	r=0.59 p< 0.01
LV dias volume (cm^3)	p=0.10	r=0.59 p< 0.01

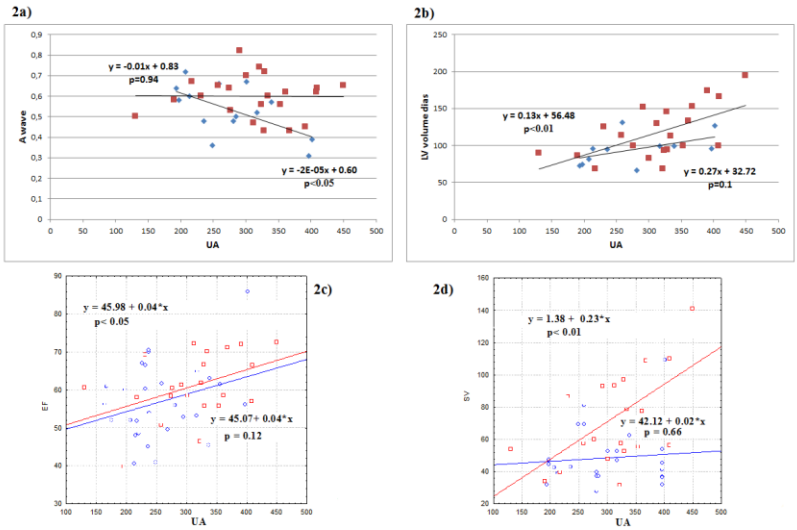
ns - not significant. LA = Left atrium, LV = Left ventricular; IVS dias - Enddiastolic interventricular septum thickness; LV dias Enddiastolic diameter; IVS sys - Endsystolic interventricular septum thickness, LVM- LV mass; LVMIV LV mass indexed to body height$^{2.7}$, E wave - peak early transmitral filling wave velocity velocity; A wave - peak late transmitral filling wave velocity ; EF - Ejection fraction; SV - stroke volume, LV volume dias- LV volume in diastole.

Figure 1:-Correlations between UA and LV structural echocardiographic parameters



None of the correlations differed between the 2 groups. Red dots - Overweight and Obese, Blue dots - Lean control, IVS dias - Enddiastolic interventricular septum thickness, LVM- LV mass, LA-Left atrium.

Figure 2:-Correlations between UA and LV functional diastolic and systolic echocardiographic parameters



Difference between study groups in correlation of SV and UA: $p<0.05$. Other correlations did not differ between the 2 groups. Red dots - Overweight and Obese, Blue dots - Lean control, A wave - Peak late transmitral filling wave velocity velocity; EF - Ejection fraction; SV - stroke volume, LV volume dias- LV volume in diastole.

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