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Excessive Weight and Obesity Are Associated to Intra-Ventricular Asynchrony: Pilot Study

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Background: Excessive weight and obesity (EwO) are independent factors in the development of heart failure; they lead to a state of myocardiopathy via inflammatory and hormonal mechanisms. If excessively accumulated, epicardial fat favors a pro-inflammatory state. Ventricular asynchrony is a marker of heart failure progression and has been poorly studied in EwO. The objective was evaluate the relation between epicardial fat, body mass index (BMI) and mechanical synchrony measured by echocardiography, in healthy individuals with EwO.

Methods: We included 55 healthy individuals between the ages of 18 and 35, 17 had a BMI < 25 kg/m^2 (30.9%) and 38 had a BMI > 25 kg/m^2 (EwO group) (69.09%), anthropometric measurements, transthoracic echocardiogram and synchrony evaluation were obtained.

Results: Left atrial volume, telediastolic and telesystolic left ventricular volumes and the baseline volume of the right ventricle were greater in the EwO group (20 mL/m^2 vs. 15 mL/m^2, p = 0.001; 106 mL vs. 82 mL, p = 0.0149 vs. 32 mL, p = 0.001 and 34 mm vs. 31 mm, p = 0.02, respectively). The Yu index also correlated with epicardial fat, r = 0.53, p < 0.01, whereby the greater the amount of epicardial fat, the greater the dispersion timing of ventricular activation. The systolic synchrony index also correlated with the BMI, p = 0.01.

Conclusion: Mechanical intraventricular asynchrony is associated to EwO and the amount of epicardial fat; hence, asynchrony may be one more factor leading to heart failure in EwO individuals.

KEY WORDS: Excessive weight · Obesity · Intraventricular asynchrony.

Introduction

The prevalence of excessive weight and obesity (EwO) has increased worldwide, and the problem includes Mexico.[1)2)] EwO are known independent factors in the development of heart failure[3-5)] since they lead to a cardiomyopathy state through inflammatory and hormonal mechanisms as a result of cardiac steatosis; this refers to the pathological accumulation of triglycerides in myocytes which in turn, leads to reactive oxygen species release that foster fibrosis formation, hypertrophy and myocardial apoptosis.[6)] Moreover, excessive accumulation of epicardial fat fosters a pro-inflammatory state.[7)]

Also, individuals with EwO develop a hyperdynamic state that in the long-run, leads to ventricular remodeling and dysfunction.[8)] Ventricular remodeling and dilation may condition mechanical asynchrony, a marker reflecting heart failure progression in several populations.[9)] Previous studies have documented the presence of interventricular asynchrony in female obese, diabetic patients.[10)] Schuster et al.[11)] demonstrated the existence of intraventricular asynchrony in 10 morbidly obese individuals but that reverted after 8 weeks of physical training.

Echocardiography is useful in the evaluation of synchrony, both by tissue analysis (tissue and speckle tracking) as well as in its tridimensional modality. It is also a validated method in the evaluation of epicardial fat.[12)13)]

The aim of this study was to evaluate mechanical synchrony in subjects with EwO compared with eutrophic individuals, as well as to analyze the relation between the linear quantity of epicardial fat–determined by echocardiography–and ventricular mechanical synchrony.

METHODS

We included subjects between the ages of 18 and 35. We obtained a complete clinical history, electrocardiogram and conventional transthoracic echocardiogram. Participants with a normal physical examination, electrocardiogram and baseline echocardiogram were included. Those with a history of heart disease or any other relevant pathology, receiving any type of drug or harboring an infection, were excluded; subjects with a sub-optimal acoustic window or that refused to participate in accordance with the informed consent were also excluded. All individuals were asked to fast for 8 hours before the procedures, and this study was approved by our institutional ethics committee and all the participants gave informed consent.

Participants were divided into two groups according to their body mass index (BMI): subjects with a BMI > 25 kg/m^2 were cases and formed the EwO group while subjects with a BMI ≤ 25 kg/m^2 were controls. Excess weight was defined as a BMI > 25 but < 30 kg/m^2, and obesity reflected a BMI greater than 30 kg/m^2.

ANTHROPOMETRIC MEASUREMENTS

Weight (W): obtained in a single well-calibrated scale while only wearing a hospital gown. Height (H): measured with the patient barefoot, with his back to the stadiometer. Body circumferences were obtained with a flexible measuring tape in centimeters. The abdominal perimeter was measured at the mid-point between the inferior costal margin and the iliac crest. Hip circumference was measured in three points: posterior (maximum gluteal extension), anterior (at the pubic level), and lateral (at the level of the femoral greater trochanters). An average of all three measurements was considered for the study's purposes.

ECHOCARDIOGRAPHIC STUDY

An IE33 echocardiography machine (Philips, Andover, MA, USA), was used, with a 5x Matrix transducer and Q-Lab version 9.0. Based on the guidelines,[14)] conventional echocardiograms were obtained. Interventricular (VV) synchrony evaluation: it was studied with pulsed Doppler of the outflow tracts; it is defined as the time difference in onset of flow between both ventricles and is determined as the time period from the initiation of the QRS complex to the initiation of left ventricular flow onset vs. that of the right ventricle. Atrio-ventricular

(AV) synchrony, the percentage of time occupied by ventricular filling in the cardiac cycle, was also evaluated with pulsed Doppler of the mitral valve. Intraventricular synchrony, the analysis of the regional time periods of ventricular mechanical activation, was measured by color-coded tissue characterization, following the recommendations of a consensus of experts.[15)] Peak systolic velocity, time between the electrocardiographic Q wave and the systolic peak (Q-S time), and the time between the electrocardiographic Q wave and the beginning of the e' wave, were measured in the basal and mid-segments of 4, 3, and 2 chambers (total of 12 segments). The standard deviation of the Q-S times in the 12 segments was obtained in order to calculate the Yu index.[16)] Longitudinal strain was obtained in bidimensional images of the same projections. The systolic synchrony index (SSI) was calculated on the basis of the three-dimensional (3D) complete volume acquisition that is, the analysis of time dispersion vis á visa minimal regional volume of 16 segments.

MEASURE OF EPICARDIAL FAT

Standard parasternal long-axis and short-axis views from two-dimensional (2D) images were obtained. Epicardial fat was identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of pericardium; Epicardial fat thickness can be also appear as hyper-echoic space, if in large amount (> 15 mm). Its thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in 3 cardiac cycles at the point on the free wall of the right ventricle at which the ultrasound beam is oriented in a perpendicular manner, using the aortic annulus as an anatomic landmark. For midventricular parasternal short-axis assessment, maximum epicardial fat thickness was measured from 2D images on the right ventricular free wall along the midline of the ultrasound beam perpendicular to the interventricular septum at mid chordal and tip of the papillary muscle level, as anatomic landmarks.[13)]

STATISTICAL ANALYSIS

According to their distribution, continuous variables were expressed as means and standard deviations or medians and minimum-maximum intervals; comparisons were obtained with Student's t test or Mann-Whitney's U test, respectively. Categorical variables were compared with Fisher's exact test. The relation between variables was analyzed with Pearson's coefficient and potential confusers, by multiple lineal regression. A $p < 0.05$ was considered significant.

RESULTS

A total of 55 subjects were included in the study; 17 (30.9%) were controls (BMI < 25 kg/m^2) and 38 (69.09%) were cases (BMI ≥ 25 kg/m^2). The average age of the case group was 30 and that of controls, 26 ($p = 0.017$). Table 1 summarizes anthropometric measurements, past history and the main findings in

the baseline electrocardiogram and echocardiogram. Epicardial fat was greater in the EwO group, $p = 0.001$. Left atrial volume was different in both groups, also being greater in the EwO group, $p = 0.001$. Furthermore, the systolic and diastolic ventricular volumes as well as the baseline right ventricular diameter were also greater in the EwO group.

Using conventional criteria in the evaluation of synchrony (responders criteria), we found neither intraventricular asynchrony according to Yu's index, no SSI, and no AV nor VV asynchrony in either group (Table 1).

There was a correlation between the amount of epicardial fat and the BMI, $r = 0.78$, $p < 0.001$. The relationship between epicardial fat and Yu's index was $r = 0.53$, $p < 0.001$ (Fig. 1). Finally, we established that the greater the BMI, the greater the SSI, $r = 0.48$, $p < 0.001$ (Fig. 2).

Inter-observer reproducibility was evaluated between the two echocardiographists participating in the study: there was good concordance, with an intra-class correlation coefficient of 0.75, in the determination of peak systolic velocity, 0.86 in the Q-S time estimates, 0.97 in the SSI and 0.88 in the 3D left ventricular ejection fraction. Bland-Altman analysis of Yu's index proved that measurements by both echocardiographists were similar (difference of -1.81 ms, $p = 0.289$).

DISCUSSION

This study, for the first time, demonstrates that there is an association between the BMI, the amount of epicardial fat and intraventricular mechanical asynchrony. Since both epicardial fat and BMI related to the time dispersion of the ventricular contraction as measured with Yu's index, this suggests that

Table 1. Anthropometric measurements, baseline electrocardiogram and echocardiogram

	BMI < 25 (n = 17)	BMI ≥ 25 (n = 38)	p
Age (yrs)	26 (18–32)	30 (18–35)	0.017
Males, n (%)	7 (41)	9 (24)	0.20
Weight (kg)	62 (40–79)	82 (62–150)	< 0.001
BMI (kg/m^2)	22 (18–24)	28 (25–52)	< 0.001
Waist (cm)	80.2 ± 8.8	99.5 ± 16.2	< 0.001
Hips (cm)	96.6 ± 6.1	107.1 ± 10.0	< 0.001
Smoking, n (%)	0 (0)	1 (3%)	0.5
Systemic arterial hypertension (%)	0 (0)	1 (3%)	0.5
QRS duration (mseg)	6.6 (6–7)	6.7 (6–8)	0.78
Echocardiogram findings			
LVDD (mm)	42.3 ± 3.7	43.3 ± 4.1	0.38
LVSD (mm)	29.0 ± 3.9	28.5 ± 5.0	0.83
Relative thickness	0.37 (0.29–0.47)	0.39 (0.29–0.58)	0.13
Left ventricular mass (gr/m^2)	58 ± 10.1	60 ± 12.7	0.63
Long axis fat (mm)	2 (1.4–4.3)	3 (1.4–7.2)	0.0001
Short axis fat (cm)	2.2 (1.7–3.8)	3 (1.6–7.9)	0.001
E/e' ratio	4.8 (3–8)	5 (3.5–8.5)	0.23
PASP (mm Hg)	22.9 ± 5.3	23.0 ± 6.1	0.94
TAPSE (mm)	22.5 (21–31)	22 (16–30)	0.14
Tei RV	0.37 (0.33–0.4)	0.4 (0.35–0.46)	0.10
LVEF (%)	67 (60–69)	61 (58–65)	0.07
3D LVEF (%)	58 (56–69)	58 (53–64)	0.11
3D telediastolic volume (mL)	82.3 ± 28	105.9 ± 27.8	0.01
3D telesystolic volume (mL)	32.8 ± 13.2	49.1 ± 15.8	0.001
LA volume (mL/m^2)	15 (12–17)	20 (18–26)	< 0.001
Baseline RV diameter (mm)	30.9 ± 5.8	34 ± 3.5	0.02
Filling time (%)	53 (50–55)	53 (50–59)	0.60
Differences in ejection periods (msec)	3 (-45–25)	-3.5 (-32–32)	0.80
GLS (%)	-18.2 ± 2.0	-16.9 ± 2.0	0.05
3D dyssynchrony index	1.9 (0.86–5.1)	2.32 (0.61–11.5)	0.46
Yu index (ms)	9.1 (4.5–31)	11.6 (22–45.2)	0.07

BMI: body mass index, LVDD: left ventricle end diastolic diameter, LVSD: left ventricle end systolic diameter, PASP: pulmonary arterial systolic pressure, LVEF: left ventricular ejection fraction, 3D LVEF: tridimensional left ventricular ejection fraction, LA volume: left atrial volume, GLS: global longitudinal strain, TAPSE: tricuspid annular plane systolic excursion, RV: right ventricle
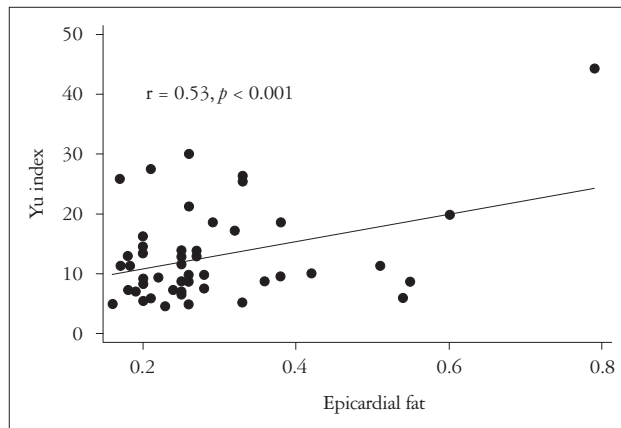
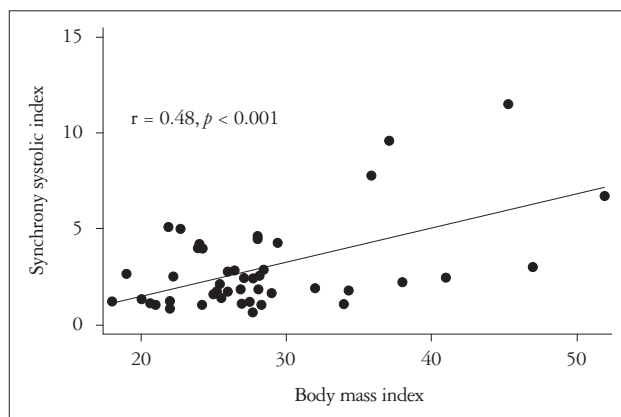**Fig. 1.** Relationship between Yu index and epicardial fat.

Fig. 2. Correlation between synchrony systolic index and body mass index.

the greater the amount of epicardial fat and BMI, the greater the ventricular asynchrony. This supports the theory that ventricular asynchrony is another pathophysiological mechanism that may contribute to the ventricular dysfunction of obesity cardiomyopathy. Other authors have reported that VV asynchrony correlates with the amount of body fat.[17] Intraventricular asynchrony was described in a study previous to ours, in 2 patients with morbid obesity and it reverted after weight loss.[18] In Kramer's study in mice, obesity was shown to cause intraventricular asynchrony and decrease strain and torsion.[19]

The heart's electrical activity is a quick process that occurs in the first 40 milliseconds and is followed by the synchronic mechanical activation of all myocardial segments. Pathological entities inducing abnormalities in its structure and function may lead to dispersion in the timing of ventricular contraction reflecting the fact that some ventricular regions contract earlier while others do so later within the same cardiac cycle.[20]

In EwO, there are structural myocardial changes resulting from the excessive intracellular accumulation of free and intermediate fatty acids such as ceramides, both toxic and contributors to cardiomyocyte death through oxidative and non-oxidative pathways; they also generate fibrosis.[7)21)22)] Therefore, the amount of intra-myocardial lipids leading to cardiac ste-

atosis contributes to cardiac dysfunction.[23-25]

Obesity also affects the hemodynamic behavior of the heart[8] by increasing the total circulating volume; obese individuals thus have an increased cardiac output.[8)26)] This study found that patients with EwO have significantly larger intra-cavitary volumes when compared with controls. The amount of adipocytes within myofibrils is associated with a greater ventricular mass[23)27)] but our study did not reveal greater myocardial mass; this may result from the fact that most of our participants only had excess weight while in other studies, obese individuals were predominant. This suggests an evolutionary sequence of events in obese cardiomyopathy in which the first step is an increase in cavity volumes followed by an increase in ventricular mass; this second step could well be an advanced marker of pathological ventricular remodeling. Krishnan et al.[28] analyzed this same concept and concluded that cavity dilation in conjunction with an increased ventricular mass are part of a sequence of events that culminate in ventricular dysfunction. An early sign of this ventricular dysfunction is the presence of abnormalities in the deformation and the longitudinal strain rate;[29)30)] our findings are in agreement since we detected a decrease in the myocardial longitudinal strain properties in our EwO group.

The mechanisms by which obesity leads to heart failure are multiple, ranging from hemodynamic, metabolic and inflammatory abnormalities to the direct toxic effect of adipocytes on the myocardium.[7)31)32)] We can now further suggest that intraventricular asynchrony is another implicated mechanism.

Finally, we must emphasize that this study did not include patients with associated confusers such as hypertension or diabetes, among others, so the observed differences are explained by EwO, and underscore the impact of these diseases on the myocardium.

STUDY LIMITATIONS

The study was primarily conducted in subjects with excess weight and there are few obese individuals; this results from the difficulty in recruiting obese subjects with no associated comorbidities. The cohort number needs to be increased to confirm these observations and understand the long-term impact of our results.

CONCLUSION

Intraventricular mechanical asynchrony is associated to both EwO and the lineal amount of epicardial fat as measured by echocardiography; hence, intraventricular asynchrony may be one more pathophysiological component implicated in the evolution to heart failure in the EwO population.

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