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Assessment of left atrial functions in cardiac syndrome X

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Abstract. – OBJECTIVE: Cardiac syndrome X (CSX) affects left ventricular functions due to myocardial ischaemia. In this study our aim was to determine the changes in left atrial functions in patients with CSX.

PATIENTS AND METHODS: One-hundred patients (M/F; 57/43) diagnosed with CSX in whom ischaemia was detected at exercise test and myocardial perfusion scintigrapghy with normal coronary angiogram and control group of 80 subjects (M/F; 40/40) were recruited into the study. In transthoracic echocardiography and tissue doppler echocardiography, left ventricular and atrial functions were recorded.

RESULTS: As compared to control group,left ventricular diastolic functions were impaired (E/A; 0.95 ± 0.18 vs 1.11 ± 0.29 $p < 0.001$), left ventricular end-diastolic pressures were increased (E/Em; 8.1 ± 1.85 vs 6.9 ± 1.74 $p < 0.05$), and left atrial maximum volume, left atrial pre-A volume,left atrial minimum volume were increased in patients with CSX. Left atrial conduit volume was significantly decreased in patients with cardiac syndrome. Left atrial passive emptying volume (LAPEV), left atrial active emptying volume (LAAEV) and left atrial total emptying volume (LATEV) were significantly increased in patients with cardiac syndrome X. Left atrial passive ejection fration (LAPEF) was found similar between the study groups.Left atrial active ejection fraction (LAAEF) was found significantly increased (37.85 ± 11.89 vs 33.60 ± 9.21; $p = 0.009$) in patients with CSX. Left atrial total ejection fraction (LATEF) was increased in the group with cardiac syndrome X but it didn't reach statistical significance (60.85 ± 8.73 vs 58.36 ± 8.29; $p = 0.054$).

CONCLUSIONS: Left atrial active contractile pump function increase in response to impaired left ventricular diastolic functions in CSX. Increased left atrial pump function represents a compensatory mechanism in patients with CSX. These results point out the importance of maintaining sinus rythm in patients with CSX.

Key Words:
Coronary artery disease, Cardiac syndrome X, Left atrial function, Left ventricular Diastolic function.

Introduction

Cardiac Syndrome X (CSX) is a clinical entity characterized by angina-like chest discomfort, positive treadmill exercise test and angiographically normal coronary arteries[1,2]. Myocardial ischemia due to coronary microvascular endothelial dysfunction and increased sensitivity to pain are the mechanisms predominantly considered to be responsible from the pathophysiological process, while reasons such as insulin resistance, estrogen deficiency, and autonomous dysfunction are also being discussed in etiology[3]. Intravascular ultrasound studies, coronary arteries with atheromatous plaques or abnormal coronary arteries with intimal thickening were detected in patients with CSX[4]. These findings prompted clinicians to consider CSX as an early phase of atherosclerosis[5,6]. Left ventricular (LV) diastolic dysfunction (LVDD) is considered as an early finding in atherosclerotic coronary artery disease[7] and during LVDD, the left atrial (LA) functions are affected.

The LA chamber is not a simple transport gap but also has a dynamic structure. LA function includes LA expansion during LV systole (reservoir phase), passive (conduit phase) and active (booster or contractile phase) left atrial emptying during early and late LV diastole[9-13]. Two-dimensional and tissue Doppler imaging at different phases of the cardiac cycle have been successfully used in measurement of LA volume and various LA functions[14,15].

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In this study our aim was to investigate LA volume and functions in patients with CSX. To our knowledge, no study has evaluated left atrial mechanical functions in patients with CSX with preserved LV systolic function.

Patients and Methods

Patient Population

This study was designed as a cross-sectional and observational study. One-hundred patients diagnosed with CSX who were admitted to our hospital and a control group of 80 subjects were recruited into the study between March 2012 and December 2013, after the approval of local Ethics Committee. CSX was defined as typical chest pain during rest or effort, abnormal test result for exercise ECG and myocardial perfusion scintigraphy, and presence of angiographically normal epicardial coronary arteries. Control group was selected from volunteers presented to our hospital with the complaint of atypical angina who had normal result from exercise ECG and had similar risk profile with the patients (diabetes, hypertension, age, gender). Patients with valvular heart disease (mitral stenosis and moderate to severe mitral regurgitation, moderate to severe aortic stenosis and regurgitation including mitral annular calcification), heart failure (left ventricular ejection fraction < 50%), congenital heart disease, cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, cardiac surgery, thyroid disease, anemia, infectious or pulmonary diseases were not included. Body weight was measured using calibrated electronic scales. Body surface area (BSA) was calculated by the Du Bois[16] formula: BSA (m^2) = 0.007184 × height (cm)$^{0.725}$ × weight (kg)$^{0.425}$. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Both patient and control groups were clinically examined and evaluated with rest electrocardiography.

Patients performed the exercise treadmill tests with the original Bruce protocol[17]. The target heart rate was calculated by the formula: target heart rate = (220-age) × 0.85. The 12-lead electrocardiogram (ECG) was recorded before exercise test and the real-time ECG and blood pressure were monitored during the whole process of exercise test. ECGs were recorded every 2 minutes since the exercise stopped till 10 minutes. The main criteria for stopping the exercise were: reaching the target heart rate, unreleasing chest pain or failing for fatigue. Results meet one of the following criteria were considered positive: chest pain; visually horizontal or down-slope ST-segment depression ≥ 0.1 mm 80 ms after J junction for 2 minutes; ST-segment arcade elevation ≥ 0.2 mm for 1 minute or severe arrhythmias.

Echocardiographic Study

All patients received a comprehensive echocardiographic examination using a Vingmed Vivid Seven Doppler echocardiographic (GE Vingmed Ultrasound, Horten, Norway) unit with 2.5 MHz FPA probe. During echocardiography, a one-lead electrocardiogram was recorded continuously. During the transthoracic echocardiographic examination the left atrium and the left ventricle (LV) were measured in M-mode according to the recommendations of the American Society of Echocardiography[18]. LV ejection fraction (LVEF) was calculated with the modified Simpson's method by measuring the left ventricular end-diastolic and end-systolic volumes with apical four-chamber view[19]. LV mass (LVM) was calculated according to the formula of Devereux et al[20]; LVM = 0.8 × (1.04 × [(LVEDD + IST + PWT)3 – (LVEDD) 3]) + 0.6 g and then divided by the body surface area to obtain the LVM index (LVMI). LVH was defined by increase in LVMI > 95 g/m^2 in women and >115 g/m^2 in men[21]. Doppler echocardiographic recording allowed analysis of the diastolic mitral flow velocities of the E-wave(m/s), the A-wave (m/s), the E/A ratio). Left atrial volumes (LAV) were measured using the modified Simpson's biplane method as orthogonal apical 2- and 4-chamber views[22,23]. Three types of LA volume were determined: maximal LA volume (LAV_{max}) at the LV end-systolic phase just before mitral valve opening, preatrial contraction LA volume (LAVpreA) at the beginning of P-wave on the ECG, and minimal LA volume (LAV_{min}) at the LV end-diastolic phase just after mitral valve closure. LAV_{max}, LAVpreA and LAV_{min} were then divided by the body surface area to obtain the volume indices. Left atrial Total EF (reservoir function), left atrial passive EF (conduit function), and left atrial active EF (booster pump function) were calculated as indices of global LA phasic function. LA reservoir function was assessed using total emptying volume (TEV) = $LAV_{max} - LAV_{min}$ and the LA Total EF (LATEF) = ($LAV_{max} - LAV_{min}$)/LAV_{max} × 100. LA conduit function was assessed by calculating the atrial conduit volume (LACV), the atrial passive emptying volume

(LAPEV) = LAV_{max} – LAVpreA and the LA passive EF (LAPEF) = (LAV_{max} – LAVpreA)/LAV_{max} × 100. LA booster or contractile function was assessed by calculating the left atrial active emptying volume (LAAEV) = LAVpreA – LAV_{min} and the left atrial active EF (LAAEF) = (LAVpreA – LAV_{min})/LAVpreA × 100[24].

The pulsed wave Doppler tissue imaging (DTI) sample volume (2 mm axial length) is placed on mitral annulus at the lateral LV wall in the apical four-chamber view. Special attention was paid to align the Doppler beam paralel to the LV lateral wall to optimise Doppler measurements. Measurements are obtained during end expiration, at a sweep speed of 100 mm/s and an average of three beats is measured. The Nyquist limit is set at a range of 20 to –20 cm/s with minimum gain and low filter settings to optimise the spectral display. Previous studies have demonstrated that there is no significant difference between the basal septal and basal lateral peak A velocity, unlike the early diastolic E velocity[25]. Peak diastolic early filling and atrial contraction velocities derived from DTI were measured offline. The ratio of early diastolic transmitral inflow velocity to annular tissue velocity (E/E) were measured and E/E was used as an index of LV diastolic function.

Statistical Analysis

Descriptive statistics are given in the mean ± standard deviation form. Normal distribution was tested with one sample Kolmogorov-Smirnov test. Comparison of the two groups for normally distributed data was performed with *t*-test; Mann-Whitney U test was used for the data whose were not normally distributed. Relationships between variables were examined by Pearson's correlation coefficient. The level of significance set at = 0.05. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS version 20.0, SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the patients participating in the study are shown in Table I. Between the study group of CSX and control group, there was no significant difference for gender, age. Heart rate, systolic and diastolic arterial pressures, history of smoking, hypertension, fasting glucose levels, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) levels.

The echocardiographic parameters of the group of CSX and control group are shown in Table II. No differences were noted between the groups for LVESD, LVEDD, LVMI and LVEF. In the transmitral Doppler analysis, E-wave was lower in CSX group compared to the control group. A-wave was non-significantly lower in patient group with CSX compared to the control group. In the tissue Doppler analysis of the mitral annular velocities, Sm was not different between the study groups. Em was significantly lower in patients with CSX compared to the control group (0.10 ± 0.02 vs 0.15 ± 0.05; re-

Table I. Demographic and biochemical characteristics of study groups.

	CSX	Control group	p
Number of subjects	100	80	
Men/women	57/43	40/40	NS
Age (years)	48.6 ± 9	47.5 ± 6	NS
BSA (m^2)	1.75 ± 0.22	1.79 ± 0.14	NS
Systolic blood pressure (mmHg)	119.6 ± 11.2	120.1 ± 10.6	NS
Diastolic blood pressure (mmHg)	72.7 ± 8.6	74.2 ± 7.4	NS
Heart rate (bpm)	73 ± 6	74 ± 9	NS
BMI (kg/m^2)	27.7 ± 3.6	26.4 ± 2.9	NS
Glucose (mg/dL)	95.2 ± 6.4	93.5 ± 4.2	NS
Total cholesterol (mg/dL)	184.2 ± 47.0	177.3 ± 45.4	NS
HDL cholesterol (mg/dL)	42.5 ± 10.0	47.5 ± 12.7	< 0.05
LDL cholesterol (mg/dL)	103 ± 32.1	100.5 ± 24.2	NS
Triglyceride (mg/dL)	174.3 ± 43.0	167.8 ± 36.1	NS
Smoking (n, %)	31 (31%)	26 (32%)	NS
Hypertension (n, %)	32 (32%)	24 (30%)	NS
Diabetes mellitus (n, %)	15 (15%)	17 (21%)	NS

NS: Non-significant.

Table II. Echocardiographic parameters in study groups.

Group	CSX	Control group	p
LVDD (cm)	4.67 ± 0.32	4.42 ± 0.36	NS
LVSD (cm)	3.02 ± 0.29	2.91 ± 0.39	NS
IVS Thickness (cm)	1.14 ± 0.05	1.13 ± 0.03	NS
EF (%)	60.16 ± 2.89	61.02 ± 3.02	NS
LVMI (g/m^2)	59.4 ± 6.4	58.2 ± 7.9	NS
LA diameter (cm)	3.58 ± 0.22	3.39 ± 0.13	< 0.001
$LAVI_{max}$ (mL/m^2)	19.66 ± 7.90	14.12 ± 1.80	< 0.001
$LAVI_{min}$ (mL/m^2)	7.7 ± 3.44	5.80 ± 1.09	< 0.001
LAVIpreA (mL/m^2)	12.53 ± 5.32	8.82 ± 1.67	< 0.001
LATEV (mL)	11.96 ± 5.19	8.31 ± 1.98	< 0.001
LAPEV (mL)	7.13 ± 3.21	5.29 ± 2.20	< 0.001
LAAEV (mL)	4.88 ± 2.29	3.01 ± 1.11	< 0.001
LACV (mL)	13.03 ± 6.32	18.37 ± 5.17	< 0.001
LATEF (%)	60.85 ± 8.73	58.36 ± 8.29	0.054
LAPEF (%)	36.68 ± 9.05	36.75 ± 12.36	NS
LAAEF (%)	37.85 ± 11.89	33.60 ± 9.21	0.009
Mitral-E (m/s)	0.78 ± 0.13	0.74 ± 0.15	0.053
Mitral-A (m/s)	0.83 ± 0.15	0.68 ± 0.6	< 0.001
E/A	0.92 ± 0.18	1.11 ± 0.29	< 0.001
Mitral E dec. time (ms)	188.5 ± 27.3	192.4 ± 21.2	NS
Mitral A dec. time (ms)	98.73 ± 21.8	99.5 ± 12.8	< 0.05
Tissue Doppler-derived parameters			
E′ (m/s)	0.10 ± 0.025	0.13 ± 0.09	< 0.05
A′ (m/s)	0.10 ± 0.027	0.12 ± 0.06	< 0.001
E/E' ratio	8.1 ± 1.85	6.9 ± 1.74	< 0.05

NS: Non-significant.

spectively, $p = 0.014$). Am was significantly lower in patients with CSX compared to the control group (0.10 ± 0.02 vs 0.12 ± 0.03; respectively, $p = 0.032$). The left atrial dimensions were significantly higher in the patient group with CSX. Indexed maximum left atrial volume ($LAVI_{max}$), indexed preatrial contraction volume (LAVIpreA) and indexed minimum left atrial volume ($LAVI_{min}$) were increased in the patient group with CSX when compared to the control group. The LATEV was significantly increased in patient group with CSX when compared to the control group. LATEF was non-significantly inreased in patient group with CSX as compared to the control group ($p = 0.052$). While LAPEV was significantly increased in patient group with CSX when compared to the control group, LAPEF was not statistically different between the study group with CSX and control goup. LAAEV was significantly increased in the group with CSX as compared to the control group. The LAAEF was significantly increased in the group with CSX as compared with the control group (Table II). While LVSV was fairly decreased in the patient group with CSX compared to the control group, LACV was significantly decreased in the patient group with CSX as compared to the control group (Table II).

The following correlations were found: 1-SBP was negatively correlated with Mitral-E velocity ($r = -0.35$, $p < 0.001$), positively corralated with Mitral-A velocity ($r = 0.34$, $p < 0.001$), negatively correlated with E/A ratio ($r = -0.45$, $p < 0.001$) and positively correlated with LATEV ($r = 0.20$, $p < 0.05$). 2- DBP was positively corralated with Mitral-A velocity ($r = 0.23$, $p < 0.005$), positively correlated with LAAEF ($r = 0.15$, $p < 0.05$), positively correlated with E/A ratio ($r = -0.26$, $p < 0.001$). 3- LAAEF was positively corralated with LAAEV ($r = 0.69$, $p < 0.0001$), positively corralated with LATEV ($r = 0.36$, $p < 0.0001$), and positively corralated with Am ($r = 0.23$, $p < 0.01$). 4-E/Em ratio was significantly correlated with Mitral-A ($r = 0.36$, $p < 0.001$), LAAEF ($r = 0.52$, $p < 0.001$) (Figure 1).

Discussion

In this study, left atrial volumes were significantly increased in the patient group with CSX when compared to the control group. Further-

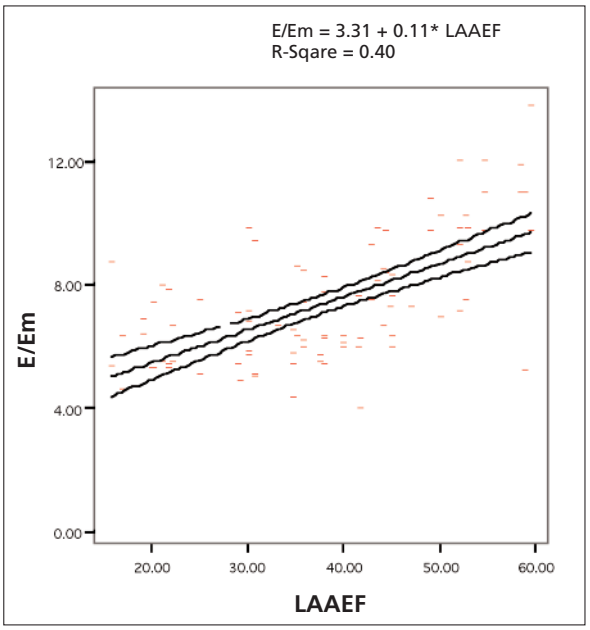

Figure 1. Correlation between E/Em and LAAEF.

more, left atrial active pump function was significantly increased in patients with CSX as compared to the control group subjects.

About twenty percent of subjects with typical anginal chest pain are found to have normal coronaries in coronary angiograms[26]. A subgroup of these patients, who also have ST-segment depression on exercise testing and myocardial ischemia on myocard scintigraphy, are classified as having CSX[27]. Endothelial dysfunction and inflammation was considered in the etiology of CSX that was proposed as an early stage of CAD[28].

LV diastolic dysfunction is significantly associated with myocardial ischemia and CAD[29,30]. As an early index of myocardial ischaemia, increased elevation of LV filling pressure induces LV diastolic dysfunction and LA enlargement[31,32]. Left atrial functions are crucial determinants of LV filling particularly when LV compliance is reduced. Left atrium modulates LV filling through its reservoir, conduit and contractile pump functions. LV stroke volume is considered to be composed of LAPEV, LAAEV and LACV[33]. In our study in the patient group with CSX, E/A ratio was significantly reduced and E/Em ratio was significantly increased in the group with CSX when compared to the control group. In the patient group with CSX, LA volumes were significantly increased as a result of increased LV end-diastolic pressures. In the early filling of the LV, the LA act as conduits passively emptying during early LV relaxation, which is strongly influenced by LV compliance. LA passive emptying function is related with multiple factors, suction force of the LV during diastole, the recoil function of the left atrium after expansion, LV end-diastolic pressure and LA pressure[34]. The left atrium is also a contractile chamber that actively empties immediately before the onset of LV systole[35]. Increased atrial contractility has been attributed to Frank-Starling law; in which increased atrial dimension leads to atrial strechening resulting in increased atrial force. Increased left atrial volumes might indicate left atrial remodelling process in response to LV diastolic dysfunction in patients with CSX. In our study, while LAPEV, LAAEV and LATEV was significantly increased in the patient group with CSX, only LAAEF was significantly different in the group with CSX compared to the control group. LAPEF was not different between the study groups and LATEF was fairly increased in the group with CSX compared to the control group (36.68 ± 9.0 vs 36.75 ± 12.75; p = 0.963 and 60.85 ± 8.73 vs 58.36 ± 8.29; p = 0.054). These results indicate that, the contractile pump function of the left atrium increases as a response of the diastolic filling impairment of the left ventricle in patients with CSX. Left atrium tries to compansate the impaired filling of the left ventricle in the patients with CSX. LA passive emptying function is related with early filling of the LV (Mitral-E) that was found similar between the study groups in our study. As an important marker of increased end-diastolic pressure of LV, E/Em, was significantly increased in patients with CSX and significantly positively coorelated with LAAEF, expresses the relationship between enhanced contractility of the LA as a compensatory mechanism and LV diastolic function.

Conclusions

In our study we found that, even in patients with ischaemic symptoms that have normal coronary angiograms, LA functions begin to adopt to the haemodynamic changes in LV. LV diastolic dysfunction and resultantly increases in LA contractile pump function are significant

consequences of the myocardial ischemia in patients with CSX. Increased left atrial pump function represents a compensatory mechanism in patients with CSX. These results signifies the importance of maintaining sinus rythm in patients with CSX.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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